RIDGE PRESERVATION FOLLOWING TOOTH EXTRACTION

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Doctor Of Philosophy

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DECLARATION

I, Neil Donald Macbeth, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below, and my contribution indicated. Previously published material is also acknowledged below.

I attest that I have exercised reasonable care to ensure that the work is original and does not to the best of my knowledge break any UK law, infringe any third party's copyright or other Intellectual Property Right, or contain any confidential material.

I confirm that this thesis has not been previously submitted for the award of a degree by this or any other university.

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ABSTRACT

Tooth extraction initiates a complex bone modelling and remodelling process, leading to undesirable vertical and horizontal topographic changes. Alveolar Ridge Preservation (ARP) techniques have been developed, to promote physiological healing at the alveolus, reducing the bone and soft-tissue dimensional change, enabling future implant placement. Unfortunately, the outcomes associated with ARP procedures are inconclusive.

The PhD was designed to compare linear and cross-sectional alveolar ridge dimensions, mucosal characteristic, composition of new bone and implant outcomes measures, following ARP. Unassisted socket healing acted as the Control.

The study used two systematic reviews, to answer the questions: Does ARP following tooth extraction improve implant treatment, and what are the hard and soft tissue changes following ARP at 4-months healing. The reviews indicated ARP did not affect implant success or survival in an augmented socket. Limited evidence was present, to support the benefits of ARP in reducing the requirement for bone augmentation at implant placement. ARP was associated with preservation of the alveolar ridge height and a variable reduction in alveolar ridge width. Evidence did not identify the superiority of a particular ARP technique, when evaluating bone and soft tissue dimensional changes, gingival tissue characteristics, bone healing and patient outcome measures.

These observations led to the development of a single blinded, randomised controlled trial, that compared Guided Bone Regeneration (GBR) and Socket Seal (SS) ARP technique, with the Control. The results indicated that GBR ARP, was effective at preserving the coronal buccal socket contour, reducing the vertical, horizontal and socket-area bone dimensions, whilst stabilising soft-tissue contours and mucosal topography. SS offered an advantage in vertical contour preservation. ARP techniques resulted in less new bone formation than the Control, with GBR requiring a reduced need for further augmentation at implant placement (ANOVA-Tukey/$p<0.05$). The use of an ARP technique did not affect implant success and survival.

LIST OF MAIN ABBREVIATIONS

2D	Two Dimensional
3D	Three Dimensional
AARW	Apical Alveolar Ridge Width
AHC	Apical Horizontal Contour
APA	Alveolar Process Area
ARH	Alveolar Ridge Height
ARP	Alveolar Ridge Preservation
ARW	Alveolar Ridge Width
ASP	Alveolar Socket Preservation
BARH	Buccal Alveolar Ridge Height
BMP	Bone Morphogenic Protein
BSE-SEM	Back Scatter Electron- Scanning electron Microscopy
CAD-CAM	Computer Aided Design – Computer Aided Manufacture.
CARW	Cervical Alveolar ridge Width
CBCT	Cone Beam Computerized Tomography
CEJ	Cemento-Enamel Junction
CHC	Cervical Horizontal Contour
CSH	Calcium Sulphate Hemihydrate
CT	Computerised Tomography
CTGF	Connective Tissue Growth Factor
D	Distal
DBBM	Deproteinised Bovine Bone Matrix
DFDBA	Demineralised Freeze-Dried Bone Allograft
DICOM	Digital Imaging and Communications in Medicine
EAO	European Association of Osteointegration
EMD	Enamel Matrix Proteins
FDBA	Freeze-Dried Bone Allograft
FGF	Fibroblastic Growth Factor
FGG	Free Gingival Graft
FMPS	Full Mouth Plaque Scores
GBR	Guided Bone Regeneration
HA	Hydroxyapatite
ILGF	Insulin Like Growth Factors
M	Mesial
Mid	Middle

MSC	Mesenchymal Stem Cells
PARH	Palatal Alveolar Ridge Height
PCL	Poly-Caprolactone Scaffold
PDGF	Platelet-Derived Growth Factor
PDL	Periodontal Ligament
PGA	Polyglycolic Acid
PLA	Polylactic Acid
PMMA	Polymethylmethacrylate
PPD	Probing Pocket Depths
PRF	Platelet-Rich Fibrin
PRFM	Platelet-Rich Fibrin Matrix
PRP	Platelet-Rich Plasma
PTFE	Polytetrafluorethylene
REC	Recession
SA	Socket Area
SRT	Socket Repair Technique
SS	Socket Seal
TCP	Tri-Calcium Phosphate
TCS	Tri-Calcium Sulphate
TGF-B	Transforming Growth Factor-B
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factors
XMT	X-ray Micro-Tomography

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Introduction

Tooth Anatomy

1.1 Tooth Extraction

The extraction of a tooth in the adult dental patient is a common procedure. Following exodontia, a complex healing process takes place, to achieve closure of the wound and re-establishment of homeostasis.

The post extraction healing process involves a sequence of different phases, which includes inflammation, proliferation and the modelling and remodelling of the alveolus. These changes can result in alteration to the morphology of the alveolar ridge and the biological function of the newly formed tissue (Atwood, 1971, Lekovic et al., 1997, Lekovic et al., 1998, Hansson and Halldin, 2012, Camargo et al., 2000, Iasella et al., 2003, Schropp et al., 2003b, Botticelli et al., 2004). Bone remodelling is a process where osteoclasts and osteoblasts work sequentially in the development and synthesis of bone, where bone modelling describes the process whereby bone is shaped by the independent action of osteoclasts and osteoblasts (Sculean et al., 2019).

The effect of post-extraction ridge modelling and remodelling and its influence on the reconstruction of the edentulous site, has been reported on by many authors (Pietrokovski and Massler, 1967, Johnson, 1969, Atwood, 1979, Schropp et al., 2003a). The healing process is characterised by re-organisation of the local oral tissue, leading to shrinkage and migration of the gingival tissue margin (Tarnow et al., 1996, Jemt, 1997, Schropp et al., 2003b, Darby et al., 2009), reduction of the gingival papilla, a reduced zone of keratinised tissue, changes to the tissue bulk and recession of the buccal and palatal gingival margin position. The extensive bone dimensional changes (Demircan and Demircan, 2015, Schropp et al., 2003b), ultimately lead to a 40-60% decrease in the height and the width of the residual alveolar ridge (Johnson, 1969) and a reduction in bone volume. The alveolar bone changes are more evident on the buccal aspect, when compared to the lingual/palatal aspect (Pietrokovski and Massler, 1967). The rate of remodelling decreases 3-4 months post-extraction (Johnson, 1969, Schropp et al., 2003b), resulting in a bone and gingival tissue level that is lower than that of the neighbouring teeth, as complete regeneration of the socket site never occurs (Amler, 1969).

The bone and soft tissue modelling, and remodelling process is influenced by several systemic and local site extraction factors. These include medical status, the presence of local infection, previous periodontal disease, traumatic injury and the presence or thickness of the bone at the extraction socket site (Garg and Guez, 2011). Further remodelling of the healed residual ridge can occur because of anatomical, prosthetic, metabolic and functional forces (Atwood, 1979, Atwood, 1971), with the process recorded as continuing throughout life.

The development and popularity of implant supported restorations, in combination with a patient led desire for a fixed tooth replacement, has led to an increased interest in the changes that occur during healing and

remodelling of the extraction socket (Avila-Ortiz et al., 2019, Atieh et al., 2021, Canellas et al., 2020). Optimal positioning of the implant leads to the development of a protective (Garber, 1996) and aesthetically acceptable peri-implant gingival soft tissue collar (Belser et al., 2004, Buser et al., 2004, Kois, 2004, Keith and Salama, 2007), which may prevent long-term peri-mucositis and peri-implantitis complications (Mezzomo et al., 2011, De Lange, 1994, Bartee, 2005). For these reasons, the morphology of the healed extraction socket is considered important in the surgical and prosthodontic stages of implant treatment (Tonetti et al., 2019, De Risi et al., 2015) since preservation of the pre-extraction alveolar ridge dimensions, promotes optimum osseointegration of the dental implant and facilitates the positioning and inclination of the implant according to prosthetically driven protocol (De Lange, 1994, Belser et al., 2004). The prosthetically driven surgical protocol, uses an idealised final prosthetic tooth position to determine the correct three-dimensional (3D) spatial relationship for the implant fixture (Demircan and Demircan, 2015, Tomasi et al.,, 2010a, Huynh-Ba et al.,, 2010, Avila-Ortiz et al.,, 2014). Achieving this co-ordination, promotes an optimal functional, biomechanical, aesthetic and maintenance outcome for the patient (Saadoun and Le Gall, 1997, Buser et al., 2004, Mezzomo et al., 2011).

The retention of the alveolar and gingival structure is seen as essential to the development of an aesthetic and biomechanically stable implant and prosthetic restoration. As the average width of the alveolar ridge has been recorded at 12 mm (8.6–16.5 mm) prior to tooth extraction (Schropp et al., 2003b), with this dimension reduced to 5.9 mm (2.7–12.2 mm) 12 months later, many edentulous sites would require additional grafting to allow optimal positioning of the implant (Mecall and Rosenfeld, 1991, John et al., 2007). The risks associated with this dimensional change are particularly evident in the anterior part of the mouth, due to the presence of the thin bundle bone (Araujo et al., 2015) that may predispose for severe alveolar resorption (Fickl et al., 2008a).

Augmentation protocols have therefore been developed to promote either retention of the original bone and soft tissue contour (alveolar ridge preservation), or to counteract the post extraction physiological bundle bone resorption (Araujo et al., 2015), influencing the bone and soft tissue remodelling process. The potential to improve the morphology of the healed alveolar ridge and to augment the bone foundation, enables reconstruction of the ridge using prosthetic or implant supported solutions (Horváth et al., 2013).

1.2 Tooth extraction and its effect in the military environment

Military patients operate in a dynamic working environment, with an increased occupational risk of facial and dental trauma when deployed on active service (Zadik and Levin, 2009, Immonen et al., 2014) and when undertaking military training roles (Gassner et al., 1999). The American Joint Theatre Trauma

Registry recorded that 23% of all military trauma was associated with facial injuries, with 15% of these injured patients experiencing related dental trauma. Lin (2011) reported similar levels of dental trauma among Israeli recruits during their Military service.

Whilst protective body armour has reduced the risk of wounds to the head and torso, the face can still be exposed to direct trauma, percussive blast wave injuries, burns and indirect damage from improvised explosive devices (Shuker, 1995, Shuker, 2008). Consequently, military patients face a higher risk of traumatic damage to their dentition, with the danger that they may suffer an increased risk of endodontic complications, tooth and alveolar fracture, or avulsion (Zadik and Levin, 2009, Diangelis et al., 2012).

Damage to the oral tissues may results in the requirement for immediate emergency care, stabilisation treatment and long-term restorative management. Extraction of the dentition is often required (Diangelis et al., 2012), which leads to transition and reconfiguration of the alveolar and basal bone complex. The remodelling process can be compounded by soft tissue loss and deformity at the basal bone level, resulting in the relocation of the alveolar ridge to a more palatal or lingual position.

As the loss of the dentition can have a profound effect on the patient's psychological, functional and social wellbeing (Kiyak et al., 1990, Walton and MacEntee, 2005), a demand has arisen for a predictable and aesthetic tooth replacement, which will meet the needs of the Service individual. Dental implants are increasingly seen as a viable treatment option, as they allow for a cost effective and predictable replacement of the missing dentition, with the ability to be utilised in patients with altered muscular function and transfigured tissue morphology. Immediate and delayed Alveolar Ridge Preservation (ARP) procedures have been proposed as techniques capable of modifying the patients physiological healing process, promoting retention of the original bone and soft tissue matrix through improved healing at a tooth extraction site, facilitating the development of a superior tissue foundation (De Risi et al., 2015).

Unfortunately, a clear and ubiquitous grafting protocol for the immediate or delayed treatment of the injured patient has not been established, with uncertainty in the requirement and the clinical advantages of different ARP procedure recorded (Horváth et al., 2013, Avila-Ortiz et al., 2014a, Hammerle et al., 2012b, De Risi et al., 2015). This PhD study therefore seeks to directly compare analogous ARP techniques, assessing outcome measures according to specific and non-objective outcomes. Determining the characteristics of the different ARP treatment options will result in a more practical and effective emergency management of dental injuries and promote simplification in the surgical treatment provided (Wood and Vermilyea, 2004). It will ensure that long-term rehabilitation costs are focused on a technique associated with a reduction in the resorption to the alveolar and gingival tissue and a greater likelihood of rehabilitation success (Torabinejad et al., 2007, Zitzmann et al., 2010, Wood and Vermilyea, 2004, Bader, 2002, Christensen, 2006).

The increased opportunity to use an implant supported restoration may be particularly important in severely injured patients, as they may have injuries that leave them with reduced tissue mobility, compromised manual dexterity and extensive soft tissue defects, where alternative treatment modalities may be impractical or unsuitable. Implant treatment may therefore enhance their psychosocial wellbeing (Malo et al., 2003) and improve the chance of rehabilitation success (Kiyak et al., 1990). The potential for an extended operative time frame afforded by an ARP procedure is also important, as it will allow urgent medical rehabilitation to take place prior to the provision of implant treatment at a more convenient time.

1.3 Anatomy and physiology of the periodontium

The periodontium is a collective term describing the tooth support structures (Cho and Garant, 2000). It is composed of five tissue components, the alveolar bone, the epithelium, a fibrous connective tissue layer, the periodontal ligament (PDL) and the root cementum. The PDL provides the lymphatic drainage and blood vessels necessary for the nutrition of the cementum, bone and gingival tissue (Melcher, 1985).

The periodontium provides a support structure for the tooth, with each component having a distinct tissue architecture and composition, that acts to maintain and co-ordinate its function in the mouth. The periodontal tissues develop and function as a unit, with each extracellular matrix influencing the cellular activities of the adjacent structure, allowing pathologic changes in one compartment to influence the maintenance, repair and regeneration of the others (Maynard and Wilson, 1979, Cardoso et al., 2012).

The periodontal tissues are embryologically derived from the dental follicle, developing in association with the formation and the eruption of the teeth. The follicle originates from the neural crest of the posterior midbrain and anterior hindbrain, with the periodontium formed because of the interaction between this tissue and the underlying ectodermal tissue (Bronner-Fraser, 1995). During tooth development, the dental papilla gives rise to the odontoblasts and the dental pulp, with the dental follicle initiating the formation of the cementum, periodontal ligament and the alveolar bone (Palmer and Lumsden, 1987).

1.4 Alveolar bone

In a dentate individual, the roots of the teeth are held in position on the inferior surface of the maxilla and the superior surface of the mandibular bone by a thickened ridge of calcified tissue defined as the alveolar bone or alveolar process (*Fig. 1*). Although the alveolar process is recorded as a separate entity, there is no demarcation between it and the body of the maxilla or the mandible, with the process accounting for much of the bone volume found in the maxilla.

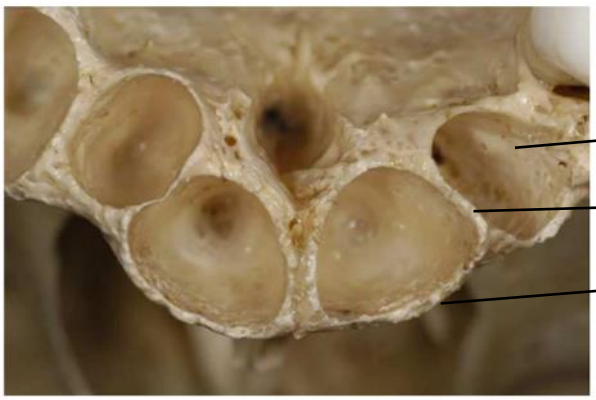


Figure 1. *Picture demonstrating alveolar process following tooth removal in a dried skull.*

The roots of the teeth are embedded within the alveolar bone, in an angular cavity or socket called the alveolus, with this bone lining considered the alveolar bone proper, as it provides direct support to the tooth. The alveolar bone proper is composed of compact and cortical bone layers and can be classified as a cribriform plate, because it contains numerous holes where Volkmann canals pass from the alveolar bone into the PDL. The alveolus is commonly referred to as the "tooth socket" and is formed by the fusion of the facial, lingual/palatal and interdental septum of the alveolar bone. The form and depth of each alveolus is determined by the geometry (Marks and Schroeder, 1996), angulation, depth and length of the root it supports and the proximity of the adjacent teeth (Ritchey and Orban, 1953).

The bony partition that separates adjacent alveoli is classified as the interdental septum. At the crest of this septa and where the separation of the roots is less than 0.5mm, the plates of the lamina dura are fused, with little intervening cancellous bone present. Inferiorly, a layer of cancellous bone is more commonly present, with 86.7% of interdental septum's showing both layers (Heins and Wieder, 1986). At sites where the root surfaces is separated by less than 0.3mm, no bone layer is present, with the roots only connected by a PDL attachment (Heins and Wieder, 1986).

The most prominent border of the interdental septa and the coronal aspect of the fused inner and outer alveolar cortical plates is called the alveolar crest. This crest is often knife edge in appearance around the anterior teeth and has a more rounded structure in the posterior molar dentition. This is due to a widening of the alveolar process in the posterior region of the mouth. The coronal aspect of the alveolar ridge runs parallel to and between 1 to 4 mm apical to the cemento-enamel junction (CEJ) (Ritchey and Orban, 1953, Braut et al., 2011, Nowzari et al., 2012, Januario et al., 2011). The CEJ represents the anatomical intersection between the cementum and enamel layers (Schroeder and Scherle, 1988), which occurs in the

cervical region of the tooth, at the junction between the root and the crown (Newman and Poole, 1974, Ritchey and Orban, 1953, Wang et al., 2014). The average distance between the CEJ and the alveolar crest was initially reported to be 1.08mm (Ritchey and Orban, 1953) with El Nahass and Naiem (2015) finding a distance of 2.10 ± 0.85mm in the central and 2.09 ± 0.72mm in the lateral incisor positions, when CBCT images were examined. Patients who had a thin gingival biotype (Cook et al., 2011) or who were smokers (Ghassemian et al., 2012), were also noted to have an increase in the distance between the CEJ to alveolar bone crest measurement.

The position of the alveolar crest was not recorded as being stable with time, with an increase in the distance between the CEJ and alveolar crest being developed following tissue changes associated with aging (Gargiulo et al., 1961, Ritchey and Orban, 1953, El Nahass and Naiem, 2015).

1.5 Periodontal ligament and bundle bone

The PDL is a uniquely dynamic (Melcher, 1985) and cellular connective tissue (Saffar et al., 1997) which contains collagen fibres, multipotent progenitor cells, fibroblasts, osteoblasts, cementoblasts and epithelial remnant cells (Gould et al., 1980, McCulloch, 1995). Neurovascular bundles navigate the periodontal ligament, consisting of vascular, lymphatic and nerve structures in a sheath.

The PDL forms an attachment to the cementum of the tooth, the periosteum tissue and the cortical alveolar bone surfaces and acts to anchor the roots of the teeth in the alveolar bone. The PDL originates in the cementum layer as thin fibril strands, which unravel as they emerge and become intermeshed with adjacent fibres, forming thicker principle fiber bundles. The principle fibres are divided into the alveolar crestal, horizontal, oblique, periapical and inter-radicular structures and are composed of 80% type I, 20% type II, and a small amount of type XII collagen (Berkovitz, 1990). The principal fibres have a complex and varying pattern of attachment, with the intricacy of the arrangement meaning that the root of the tooth is supported and protected from functional loading in any direction. The presence of oxytalan fibres running parallel to the root surface, helps to increase the rigidity of the tooth support, with some of the fibres found to insert into the cementum layer (Strydom et al., 2012).

The terminal portion of the PDL, which attaches to the alveolar bone, is described as Sharpey's fibres. The layer of alveolar bone which is perforated by the PDL and forms the attachment margin for Sharpey's fibres, is described histologically as the bundle bone. This dense, cortical bone layer is also termed the 'lamina dura' radiographically and represents the bundle bone that lies adjacent to the periodontal ligament, lining the tooth socket. The lamina dura, along with the periodontal ligament acts to distribute the oral forces placed on the dentition and plays an important role in the alveolar bone remodelling process following

extraction of a tooth. The bundle bone can occupy almost the full thickness of the alveolar process of teeth situated in the anterior part of the mouth (Araujo et al., 2015).

The cells of the PDL are active in ongoing remodelling of the ligament, cementum and alveolar bone structure. Undifferentiated ectomesenchymal stem cells which are located around blood vessels, in combination with immature fibroblasts derived from the PDL, have the potential to develop into cementoblast or osteoblast cells (Vignery and Baron, 1980, Gould, 1983, Lin et al., 1994), promoting healing and repair of the alveolar bone or root surface following damage to the tissue (Melcher, 1985). Osteoclasts and odontoclasts are responsible for resorption of the bone and tooth surface and are formed from differentiation of multinucleated cells derived from blood-borne macrophages. Activation and differentiation of the progenitor cells is regulated by an array of extracellular molecules and cytokines (growth factors) that induce both selective and non-selective responses in the different cell lineages and their precursors.

1.6 Gingival tissue

The gingival tissue is a specific part of the oral mucosa, which covers the alveolar process in the mandible and maxilla (Schroeder and Listgarten, 1997). It is comprised of two separate layers, an overlying keratinized oral epithelium and an underlying fibrous connective tissue layer (Gargiulo et al., 1961).

The gingival tissue is subdivided into two distinct regions, the marginal or free gingiva and the attached gingiva (Orban, 1948, Schroeder and Listgarten, 1997). The American Academy of Periodontology (AAP) defines the free gingiva as “the part of the gingival tissue that surrounds the tooth and is not directly attached to the tooth surface”, with the attached gingiva described as “the portion of the gingiva bound to the tooth and to the alveolar bone, extending from the free gingival groove to the muco-gingival line”. Both are continuous within the oral cavity.

There is some debate over the inclusion or exclusion of the dento-alveolar fibres in the definition of the gingival tissue. Schroeder (1997) defines the apical line of demarcation to include the apical dento-alveolar fibres at the base of the entrance of the periodontal ligament space but concedes that this attachment could be considered part of the periodontal ligament due to its tooth, bone and cementum connection.

host defence as it releases gingival cervical fluid and inflammatory cells (Genco, 1996).

1.7 Periodontal phenotype

Although the structural composition of the gingival tissue can be considered as similar in all patients, identifiable differences are often described. These differences can be quantified according to the physical characteristics and topographical structure of the tissue, or by variation in the measurement of the length and thickness of the attached keratinised tissue, the height of the interproximal papilla, the depth of the gingival sulcus or the length of the junctional attachment. These variations exist because the physical and dimensional characteristics of the gingival tissue can be affected by the size of the alveolar process, the shape of the tooth, the tooth position, characteristics of tooth eruption and the inclination and position of the fully erupted teeth (Wheeler, 1961). Other local variations can occur as a result of the age (Smith et al., 2015) and ethnicity of the patient (Muller et al., 2000, Muller and Eger, 1997, Sharma et al., 2014).

Variation in the response of the gingival tissue to inflammation, disease, surgical and prosthetic intervention and tooth extraction have been reported according to the size and dimensional characteristics of the gingival tissue (Abraham et al., 2014, Ahmad, 2005), leading researchers to attempt to classify a patient's individual risk status according to the characteristics of the gingival anatomy.

Ochsenbien and Ross (1969) examined patients following osseous surgery and identified two distinct risk groups according to their gingival characteristics. One group had a highly scalloped gingival margin and thin gingival morphology, with the other a flat margin and thick gingival tissue. Patients with a scalloped gingival margin and thin tissue were associated with a higher rate of healing complications and recession.

The term periodontal biotype was first introduced by Seibert and Lindhe (1989) who categorized the gingiva into "***thick-flat***" and "***thin scalloped***" biotypes. Olsson and Lindhe (1991) and Olssoin et al. (1993) developed this concept further, describing a patient's specific gingival morphological characteristics. Their findings suggested that subjects with long, narrow teeth and a thin periodontium, were more susceptible to gingival recession than subjects with a thick gingival biotype.

Whilst the term "gingival biotype" has been commonly used to describe the gingival tissue in the bucco-lingual dimension, the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions, strongly suggested the adoption of the definition "***periodontal phenotype***". The term periodontal phenotype describes the combination of gingival phenotype (3D gingival volume), the thickness of the buccal bone plate (bone morphotype) (Jepsen et al., 2018, Caton et al., 2018) and encompasses the tooth shape and dimensional morphological characteristics of the gingiva and the periodontium. The gingival phenotype includes the gingival thickness and keratinized tissue width, with the bone morphotype comprising the buccal bone plate thickness.

It is worth noting, that the World Workshop recommended the use a periodontal probe as a standardised and reproducible way to evaluate the gingival thickness. It advised observing whether the periodontal probe

was seen to shine through gingival tissue after being inserted into the sulcus. Thus, it was assumed that the probe will be visible when GT is thin (≤1 mm) and not visible in a thick GT (>1 mm).

Cluster analysis by De Rouck et al. (2009) and a separate World Workshop review (Cortellini and Bissada, 2018) focused on the periodontal biotype. Here the investigators considered the classification proposed by Zweers et al. (2014). The review described the presence of three periodontal biotypes, recognising a "thin-scalloped", "thick-scalloped" and "thick-flat" form.

a. Thin-scalloped: associated with a slender and triangular tooth crown, small dental cervical curvature, points of contact to the incisal surfaces, the narrow width of keratinized gingiva, thin gingiva at the CEJ, and relatively thin labial bone plate at both distances apical to the CEJ.

b. Thick and flat: more square teeth with marked cervical curvature, large contact areas between the teeth located more apically, a wide range of keratinized gingiva, thick fibrous gingiva, and relatively thick alveolar bone sheath.

c. Thick-scalloped: thick fibrous gingiva at CEJ, thin teeth, quadratic tooth form, narrow width of keratinized gingiva, highlighted wavy contour of the gingiva, thick labial bone plate.

Clarity on categorisation again came from the World Workshop 2017 and the work of Jepsen et al. (2018), who advised that whilst most historical publications use the term biotype, the biotype represents in genetics: a group of organs having the same specific genotype. A phenotype represents the appearance of an organ based on a multifactorial combination of genetic traits and environmental factors (its expression includes the biotype). The term Phenotype is therefore preferred.

Periodontal phenotype can be evaluated through clinical or radiographic assessments and can be further divided into invasive/non-invasive (for gingival thickness), static/functional (for keratinized tissue width), and bi/tri-dimensional (for buccal bone plate thickness) methods. A description of the different measurement systems is included in Chapter 3.

As an extension of this concept was proposed by Avila-Ortiz et al. (2020a), who proposed the components of the peri-implant phenotype (soft tissue and bone) as an analogous term to periodontal phenotype.

Tissue Dimensions

1.9 Bone dimensions

With the introduction of dental implant restorations, the dimensions of the alveolar bone have gained greater significance, as they represent the extent of the anatomical foundation available for fixture placement, influencing the surgical placement, augmentation requirement and aesthetic characteristics of the definitive restoration (Araujo et al., 2015, Kim et al., 2006, Tsigarida et al., 2020). Determining the morphological and dimensions characteristics of the alveolar ridge is therefore important, as it enables the operator to anticipate the anatomical risks associated with surgical procedures and allows for greater accuracy in implant planning (Araujo et al., 2015).

1.9.1 Measurement of the alveolar bone dimensions

Various intra-oral measurement techniques have been used to evaluate the dimensions of the alveolar arch in the maxillary and mandibular bone. These techniques have included direct measurements of the bone after exposure during surgical procedures (Huynh-Ba et al., 2010), manual and digital callipers measurements (Katranji et al., 2007), or rulers and periodontal probes (Schropp et al., 2003a, Spray et al., 2000). Measurements have also been recorded on study casts (Pietrokovski and Massler, 1967).

Conventional two-dimensional (2D) radiographs have similarly been used to measure anatomical dimensions. Unfortunately, studies have suggested that projection geometry, focal plane shape, differential vertical and horizontal magnification factors, and errors in patient positioning, may affect the accuracy of results (Garg and Guez, 2011, Ludlow et al., 2007).

Computerised tomography (CT) and the recent introduction of cone beam computerized tomography (CBCT) in dentistry, has led to new opportunities in the assessment of the alveolar bone and dental tissues (Cavalcanti et al., 1999). CBCT images provide an accurate, high-resolution, multiplanar image, at a relatively low radiation dosage. They are also associated with a lower biological and financial cost to the patient and researcher (Carrafiello et al., 2010, Menezes et al., 2010, Januario et al., 2011, Araujo et al., 2015).

CBCT images are based on volumetric tomography, using a 3D cone shaped x-ray beam and a 2D extended digital array, which acts as an area detector. The images are stored as a 3D digital data set and are presented to the clinical operator in three orthogonal viewing planes (axial, sagittal and coronal) established by (Feldkamp, 1984). The quality of the images produced by CBCT scans and their ability to display anatomical features and pathology is influenced by several variables. These include, the scanning unit, the field of view, the object being examined, examination time, tube voltage and amperage, soft tissue density, voxel size and the spatial resolution (Patcas et al., 2012, Molen, 2010). The voxel size is the smallest unit

of 3D measurement that can be identified by a CBCT machine and is defined by the height, width, and depth of the unit. Voxel dimensions are generally isotropic in nature (the three parameters are equal) (Spin-Neto et al., 2013) and can range in size from 0.4 to 0.09 mm. The spatial resolution of a CBCT machine, is the minimal distance that can be recorded between two different objects, with the measurement influenced by the voxel size of the machine (Kamburoglu et al., 2011). The resolution of the final image is not always limited or defined by the voxel size, as the ability to distinguish between two objects can be affected by partial volume averaging and the presence of noise and artefacts on the image (Molen, 2010). This may account for why Ballrick et al. (2008) found that a 0.2mm voxel scan can produced an image with a 0.4mm special resolution. It would also explain why CBCT measurements were not seen to be affected by variations in voxel settings, or the imaging acquisition protocol, when repeated measurements were taken on dried human mandibles (Menezes et al., 2010).

The accuracy of measurement recorded by CT and CBCT machines has been reported on by several authors. Loubele (2008) compared liner measurements taken on small-field CBCT and multi-slice CT images, finding a 0.06 mm (± 1.23) width and a -0.09 mm (± 1.64) height variation from manual alveolar bone measurements. Micro millimetre accuracy was similarly found when comparing dimensions recorded on dried skulls (Kobayashi et al., 2004, Timock et al., 2011), or pre-calibrated models (Mozzo et al., 1998). These studies indicated a low level of width (0.8–1 %) and height (2.2 %) measurement deviations (0.13 mm ±0.09) (Marmulla et al., 2005).

Although it can be concluded that CBCT systems render anatomical measurements reliably and are an appropriate tool for linear measurements (Patcas et al., 2012), this level of accuracy may not be sufficient to accurately depict small cross-sectional bone dimensions predictably. Even at small voxel dimensions of 0.125-mm and below, there is often a large variation in the standard deviation, or the limits of agreement between operator (Patcas et al., 2012, Leung et al., 2010, Cao et al., 2017, Wood et al., 2013). The interpretation difficulties, increase the risk of interpretation inaccuracies, when measuring small widths or thin bone height dimensions (Hilgers et al., 2005), alveolar bone wall thickness (Molen, 2010, Timock et al., 2011) or when examining fenestrations and dehiscence dimensions around the dentition (Leung et al., 2010, Sun et al., 2015).

The accuracy of CBCT measurements should be review with caution, when images are produced from voxel slices above 0.2mm (Timock et al., 2011, Cook et al., 2015, Wood et al., 2013, Spin-Neto et al., 2013). This is because there is a greater chance of a discrepancies in alveolar buccal bone dimensions being recorded, due to partial volume averaging and density variation effects. Partial volume averaging is influenced by the angle at which the image plane intersects the bone wall, causing the bone to appear thinner or thicker than its real dimension (Hilgers et al., 2005). This type of computation error can cause bone walls

thinner than 1 mm to all but disappear on CT scans. To decrease the effect of partial volume averaging, a decreased voxel sizes can be used, but this increases the radiation exposure to the patient and may increase the amount of noise in the image.

Bone density and Hounsfield unit values are also used as a variable in CBCT image production, as immature or newly forming bone tissue may have a reduced bone density. This would result in a less distinct appearance on CBCT images, increasing the risk of observational errors (Marmulla et al., 2005). The reduction in contrast in newly formed tissue may equally affect the accuracy of bone measurements (Molen, 2010), as the near equivalence in radiographic density of immature bone and soft in the mouth, may compounding the ability to take accurate dimension measurements (Januario et al., 2008). This phenomenon may suggest that changes in the alveolar bone volume may only be observed following 6 to 12 months of bone healing, when an increase in the bone density has occurred.

1.9.2 Variation in the dimensions of the alveolar process

Symmetry of the mandibular and maxillary bone has been found in adults with a normal occlusion (Lear, 1968, De Araujo et al., 1993), with only minor variations recorded in the bucco-lingual and mesio-distal tooth dimensions of the dentition (Adeyemi and Isiekwe, 2004). This lack of tooth size variation has resulted in a general consistency in the shape of the alveolar process and the alveolar bone coverage of the root structure (Farina et al., 2011). The size of the alveolar bone being specific to each tooth and arch position (Vera et al., 2012).

Local variations in the alveolar bone size does occur and is reported to be influenced by the patient's gender (Demircan and Demircan, 2015), menopausal status (Zhang et al., 2016), root shape (Temple et al., 2016) and tooth inclination (Nahas-Scocate et al., 2014). Although the width of the alveolar process generally increases apically along the root length, the width of the individual facial/buccal and lingual/palatal bone surfaces can be inconsistent and can also be influenced by the measurement position below the CEJ (Braut et al., 2011, Nowzari et al., 2012, Demircan and Demircan, 2015). Farina et al. (2011) indicated a ridge thickness of 7.9 mm (± 2.1) in the first premolar, 8.3 mm (± 1.8) in the second premolar, 11.1 mm (± 1.9) in the first molar and 10.6 mm (± 2.1) in the second molar positions, when a measurement was taken 1mm from the bone crest. The width of the alveolar process increased when measurements were made at 3mm and 7mm from the alveolar crest in the premolar and molar areas (Farina et al., 2011).

Becker et al. (1997) examined the shape of the alveolar bone around teeth in the anterior maxilla in dried skulls, where three different morphotype, a flat, a scalloped and a pronounced scalloped alveolar morphology were identified. Each morphotype had a measurable difference in the height of the

interproximal and mid-buccal alveolar bone height. The pronounced scallop group was recorded as having the highest interproximal bone height and the deepest mid-buccal concavity. A consistent level of bone fenestration (35%) was found in each of the morphotypes, but a higher rate of dehiscence was found in the pronounced scalloped category. These individual bone characteristics would suggest that patient with a certain morphotype, have less bone present around the dentition.

Zhang et al. (2015) recorded a mean buccal-palatal alveolar process width of 9.55mm in the central incisor position, 8.3mm in the lateral incisor and 9.62mm in the canine positions. The lateral incisor was found to have a significantly smaller alveolar width than the other anterior teeth (Zhang et al., 2015, Morad et al., 2014).

1.9.3 Maxillary buccal socket wall thickness

The thickness of the socket wall is considered particularly important in the socket healing process, as a negative correlation has been between the buccal bone thickness and the alveolar ridge resorption (Ferrus et al., 2010, Spinato et al., 2014, Tonetti et al., 2019). In this regard, it has been demonstrated that when the thickness of the buccal bone is < 1.00 mm, a mean loss in height of 7.5 mm can occurs after single tooth extraction, while in the cases of thickness socket wall above ≥ 1.00 mm, the bone height loss can reduce to 1.1 mm (Chappuis et al., 2013). The dimensional characteristics of the maxillary anterior dentition are outline in Table 1, with the dynamics of socket healing process discussed in Chapter 5.

When investigating socket dimensional characteristics, researchers have indicated significant variation and irregularity in the socket configuration. Misawa et al. (2016), Araújo et al. (2015) and Ghassemian et al. (2012) indicated that in the anterior maxilla (central incisor, lateral incisor and canine dentition), the crestal buccal bone was thin, with a smaller dimension that that of its palatal counterpart (Misawa et al., 2016, Lee et al., 2010, Nowzari et al., 2012, Araújo et al., 2015). The reduced thickness of the buccal socket wall was highlighted in the systematic review by Tsigarida et al. (2020), who concluded that few maxillary anterior teeth had a buccal socket thickness of above 1mm.

Temple et al. (2016), Tsigaridi et al. 2020 and Rojo-Sanchis et al. (2021) observed that the principal factors responsible for buccal bone thickness were tooth position, patient age, gender, ethnicity and measurement point. As the distance between the CEJ and the bone crest increased with age, Temple et al. (2016) stated that the clinical attachment loss resulted in variation in the measurement point. This physiological change accounting for some of the dimensional changes reported on by other authors. The variation in the buccal and palatal bone thickness was investigated by Araújo et al. (2015), who observed that the width of the buccal bone wall at 3 mm varied between 0.6 and 0.3 mm, whilst at 5mm and 7 mm, the corresponding

range was 0.6–1.0 mm to 0.7–1.3 mm. Rojo-Sanchis et al. (2021) indicated a mean buccal bone thickness of ≤ 1 mm (SD 0.75–1.05) around anterior teeth (incisor - canine), with a higher width > 1 mm (SD 1.09–1.96) at maxillary premolars sites (1PM and 2PM). In all teeth analysed, a thicker buccal bone plate was found at 3 mm when compared with the measurements at 1 and 5 mm from the socket margin. Tsigarida et al. (2020) indicated that the mean thickness of the cervical bone was 1.01± 0.12 in the central incisor, 0.88± 0.16mm in the lateral and 1.07± 0.26mm in the canine region, again finding thickening of the buccal bone apically.

The buccal bone plate was occasionally found be absence, leaving the root uncovered, or with local areas of bone dehiscence, fenestration and isolated concavities (Ghassemian et al., 2012, Temple et al., 2016). Zhang (2016) investigated the presence of bone concavities, finding that 41 % of central incisors, 77 % of lateral incisors, and 33 % of canines had buccal undercuts. The mean distance from the alveolar crest to the centre of the concavity was 5.84 mm (± 2.52) in the central incisors, 3.59 mm (± 2.21) in the lateral incisor, and 5.11 mm (± 2.99) in the canine region. The buccal undercut in the lateral incisor site, was closest to the alveolar ridge. The size of the undercuts was found to be 0.76mm (± 0.47) in the incisor, 0.87mm (± 0.41) in lateral incisor and 0.73mm (± 0.37) in the canine position.

Table 1. *Mean Thickness Measurements of the Buccal Alveolar Socket Wall (mm)*

Author	Deepest concavity	Depth	Thickness
Ghassemian (2012)			1.41 mm - 1.45 (cent) 1.73 mm - 1.59 (lat) 1.47 mm - 1.60 (can)
Januario et al., (2011)			0.6mm 50% less than 0.5mm
Lee et al. (2010)	3.67 ± 1.28 mm (cen) 3.90 ± 1.51 mm (l) 5.13 ± 1.70 mm (c)	3.0 mm (alveolar crest)	0.68 mm ± 0.29 (cent) 0.76 mm ± 0.59 (lat) 1.07 mm ± 0.80 (can)
Misawa et al. (2016)		3.0 mm 5.0 mm 7.0 mm	0.4 mm (± 05) 0.8 mm (±0.4) 0.9 mm (±0.7
Morad (2014)		5.0 mm (CEJ)	1.08mm (cent) 1.11mm (lat) 1.3mm (can)
Nowzari (2012)			1.05 mm (0-5.1)
Vera (2012)		1.0 mm (alveolar crest)	0.83mm (cent) 1.13mm (pre)
Araujo (2015)		3.0 mm 5.0 mm 7.0 mm	0.4mm (±0.5) Cent 0.4mm (±0.4) (lat) 0.8mm (±0.3) Cent 0.6mm (±0.4) (lat) 1.0mm (±0.7) Cent 0.7mm (±0.5) (lat)
Rojo-sanchis (2021)			≤ 1.00 mm in maxillary (cent) 0.75–1.05 mm (can) 1.00–2.00 mm (prem)
Index - (cent – central incisor / lat – lateral incisor / can- canine and prem - premolar)			

Fenestration of the buccal bone was recorded in approximately 12% of anterior teeth (Nowzari et al., 2012), with Braut et al. (2011) observing that the facial alveolar bone was absent in 25.7% of maxillary anterior teeth, when measured 4mm below the CEJ. Braut et al. (2011) also found that a further 10% of patients had no buccal bone when the mid root position was examined, and that the thickness of the facial maxillary bone was less than 1mm in 62.9% of patients when measured 4mm below the CEJ and 80.1% when measured in the mid root position. El Nahass and Naiem (2015), observed a similar result, indicating that 75% of central incisors had less than 1mm of facial bone, with Januario et al. (2011) reporting that less than 50% of teeth in the anterior maxillary, had a buccal bone wall thickness greater than 0.5mm.

The presence of a bone dehiscence or buccal concavity, and its effect on implant treatment, was investigated by Hämmerle and Tarnow (2018). Hämmerle and Tarnow (2018) indicated that even when the buccal bone was thin at placement, evidence from prospective trials and cohort studies was inconclusive as to whether the thin residual bone would support the overlying tissue over an extended period. The lack of buccal bone and its effect on aesthetic immediate implant placement was investigated by Benic et al. (2012). The investigation indicated a higher risk of bone recession when implants were placed in close proximity to facial concavities recession. The requirement for additional grafting of these sites should be considered if early implant placement is planned (Lin et al., 2018).

In summary, the thickness and contour of the buccal maxillary alveolar plate is variable (Rojo-Sanchis et al., 2021), with a buccal socket thickness of less than 1mm found in most patients. A moderate incidence of buccal socket bone fenestration and dehiscence is observed around the anterior maxillary dentition. Loss of the buccal socket wall after tooth extraction, may influence the healing and dimensional characteristics of the site, affecting a patient's ability to seek future implant treatment (Araújo et al., 2012).

1.9.4 Maxillary alveolar process height and cross-sectional area

The height of the maxillary alveolar process has been observed to vary less than other alveolar dimensional measurement and is outline in Table 2. Zhang (2015) recorded a mean process height of 18.83 mm (± 3.23) in the central incisor, 19.07 mm (± 2.53) in the lateral incisor and 18.91 mm (± 2.81) in the canine positions, indicating no significant differences in mean dimensions. Farina et al. (2011) found similar vertical measurement when examining radiographic images of the first and second premolars sites, but noticed a marked reduction in alveolar height in the first (9.1 mm ± 3.8) and second molar (9.9 mm ± 3.9) areas. Misawa et al. (2016) recorded an average height for the maxillary process of 11.5 mm (± 2.1), with the longest measurement found at the premolar site (12.2 mm ±1.6) and the shortest (10.9 mm ± 2.4) in the lateral incisor position. These measurements are shorter that other studies, but can be accounted for, as the apex of the root was taken as the starting point of the alveolar ridge. Racial and gender deference have also

been reported, with differences attributed to both anatomical difference and disease profiles (Wong et al., 2007).

The cross-sectional area (mm^2) of the maxillary alveolar process in the incisor and premolar areas was also measured by Misawa (2016). The average cross-sectional area of the alveolar process was recorded at 99.1 ± 30.1mm^2, with the largest area found in the second premolar position (119.1 mm^2 ±27.9) and the smallest area in the lateral incisor region (82.2 mm^2 ± 23.1). The overall area occupied by the alveolar bone, defined as the part of the alveolar process supporting the tooth, was 49.5 mm^2 (± 20.7).

The cross-sectional bone area was also noted to be directly affected by the loss of the buccal bundle bone. Avila Ortiz highlighted that a loss of a 0.6mm of buccal socket, equated to a 10% loss in bone area. This small percentage may ultimately affect the feasibility of future implant treatment (Avila-Ortiz et al., 2019, Troiano et al., 2018).

Table 2. *Mean Maxillary Alveolar Process Height and Cross-sectional Area (mm^2)*

Author	Alveolar bone height	Alveolar cross-sectional area
Zhang (2015)	18.83 mm^2 (±3.23) (cent) 19.07 mm^2 (±2.53) (lat) 18.91 mm^2 (±2.81) (can)	
Farina (2011)	9.10 mm^2 (±3.8) 1st molar 9.9 mm^2 (±3.9) 2nd molar	
Misawa (2016)	11.9 mm^2 (2.2) (cent) 10.9 mm^2 (±2.4) (lat) 11.7 mm^2 (can) 11.4 mm^2 (1.2) 1st prem 12.2 mm^2 (±1.6) 2nd prem	103.3 mm^2 (±32.4) (cent) 82.2 mm^2 (±23.1) (lat) 127.8 mm^2 (can) 107.0 mm^2 (±21.5) 1st prem 119.1 mm^2 (±27.9) 2nd prem
Araujo 2015	9.4 mm^2 ± 1.6 (cent, can and prem)	34% reduction anteriorly 18% posteriorly
Index - (cent – central incisor / lat – lateral incisor / can- canine and prem - premolar)		

1.10 Gingival tissue dimensions

1.10.1 Gingival tissue width

The width of the attached keratinised gingival tissue can range from 1.0 mm to 9.0 mm, with local variations recorded at different tooth positions in the maxilla. The width of the tissue was greater on the buccal aspect of the maxillary incisors, when compared to the palatal aspect, with this relationship reversed in the premolar and molar regions (Abt et al., 2012, Lang and Loe, 1972). At maxillary incisor position, the attached tissue ranged was 4.5 – 5mm (Lang and Loe, 1972), with the canine and premolar dentition

recording the narrowest buccal width of 2.5- 3.5 mm (Abt et al., 2012). These dimensions being confirmed in studies by (Bhatia et al., 2015) and Ainamo and Loe (1966).

The patient gingival phenotype may also have a direct effect on the width of the keratinised tissue, with (Vlachodimou et al., 2021) proposing a direct association between thick phenotype patients and a wide band of keratinised tissue. Whilst the systemic review by Vlachodimou et al. (2021) was inconclusive, Cortellini and Bissada (2018) recorded that a thick band of keratinised tissue was associated with a thick gingival phenotype. Fischer et al. (2015), noted an association between gingival phenotypes and gingival width in young Caucasians, when classifying patients into thick, and thin gingival groups.

1.10.2 Gingival thickness

Various invasive and non-invasive methods have been proposed to measure the gingival tissue thickness in the oral environment. These include direct measurement by callipers, trans-gingival probing (Greenberg et al., 1976), parallel profile radiographs and probe transparency methods (De Rouck et al., 2009). Although these techniques are simple and reproducible, they can be affected by the precision of the probe placement, angulation of the probe and the distortion of the tissue during the measurement (Fu et al., 2010). Ultrasonic devices (Muller and Eger, 1997, Muller et al., 2007, Kydd et al., 1971) and superimposed STereoLithography (STL) and CBCT scans (Barriviera et al., 2009), are now regarded as a viable alternative to assess gingival thickness. Ultrasonic devices appear to be the least invasive method and offer a reliability and reproducible measurement (Eger et al., 1996). However, ensuring the correct position of any of these measuring devises has been found to be difficult, with this complication, affecting the reproducibility of results. STL-CBCT assessments are recorded as being a non-invasive, reproducible and reliable alternative, which can be used to assess the gingival phenotype during healing. Whilst the technique has been found be accurate, a meticulous analysis is required, with results affected by the presence of radiographic artifacts and CBCT scan resolution (Couso-Queiruga et al., 2021).

The findings from these studies, have indicated that prior to tooth extraction, the facial soft tissue thickness in the anterior maxilla is thin in most patients, ranging between 0.5 and 1 mm (Jonker et al., 2021, Fu et al., 2010, Muller et al., 2000, Sharma et al., 2014, Borges et al., 2015). Maxillary canines and mandibular first premolars, were recorded as having the thinnest gingival tissue (0.7- 0.9 mm), with this reduction associated with a relatively high incidence of gingival recession (Eger et al., 1996, Serino et al., 1994). The average measurements recorded for the gingival margin thickness is summarised in (Table 3).

Table 3. *Mean Gingival Margin Thickness at Different Measurements Heights in the Mouth (mm)*

Author	Position	Thickness	Measurement Height
(Borges et al., 2015)	Incisor Canine Premolar	1.24mm 1.08mm 1.19mm	
(Fu et al., 2010)	Labial surface of maxilla	0.5 mm 0.57 mm	Crest 2.0 mm
(Muller et al., 2000)	Canine	0.7 mm labial 2.00 mm Palatal	4mm below the gingival margin
Barriviera et al. (2009)	Canine Premolar 2nd premolar 1st molar 2nd molar	2.92 mm 3.11mm 3.28 mm 2.89 mm 3.15 mm	Palatal
Eger et al. (1996)	Canine 2nd molar	0.8 mm 1.5 mm	
Cortellini (2014)		5.72 mm (±0.95) Thick Biotype 4.15 mm (±0.74) Thin Biotype	
Garg et al. (2017)	Canine 2nd molar	0.8 mm 1.5 mm	
Couso-Queiruga et al. (2020)		0.79 mm	
Jonker 2021	Incisor	1.6 mm (±1.3-1.9)	

1.10.3 Soft tissue contour

The aesthetic results achieved by an implant supported restoration is not exclusively associated with the retention or presence of the alveolar bone but is also influenced by the form and outline of the prosthetic crown and the topography of the surrounding peri-implant mucosal tissue. The ability to measure the soft tissue contour and mucosal characteristics is seen as important in implant outcomes, as it has a direct impact

on the surgical protocol, peri-implant mucosal health and aesthetic outcome. The measurement of the soft tissue contour and gingival thickness can be undertaken using the superimposition of STereoLithography (STL) files and CBCT images, where STL files provide a detailed representative of the characteristics of the scanned surface. STL files can be produced by either a contact stylus profilometer or an optical scanning technique. Contact systems physically trace a probe over a target dental model or impression surface, in order to capture 2D line date. Optical profilometers project light onto a target surface to capture 3D surface data, which includes 3D tomography features, flatness and roughness (Couso-Queiruga et al., 2021). Whilst both are accurate, intra-oral optical systems have now been proposed as a superior method to detect volumetric changes in the oral tissue. A number of researchers have started to adopt this technique, as it offers the advantage of being easy to apply and use, is non-invasive and is precise in application (Moghaddas et al., 2012, Tan et al., 2012, Thoma et al., 2020b).

Digital-Intra Oral Scanning Systems: Intra oral digital scanning systems are an effective and versatile way of recording contour changes in the oral cavity (Fickl et al., 2008a, Mangano et al., 2017). They use an optical profilometer system to record the surface tomography of the oral tissues, using the created digital STL file to manufacture dental models, cast restoration and record surface changes in the mouth (Zimmermann et al., 2015). The advantage of using this system is associated with less patient discomfort, time efficiency and a simplified process for the clinician. The STL files have also been used to manufacture virtual patient model (Joda et al., 2015), with digital manipulation of the 3D model, allowing operators to record and measure hard and soft tissue topographical changes in the mouth (Fickl et al., 2008b, Thalmair et al., 2013, Jonker et al., 2021, Sbordone et al., 2017).

1.11 Periodontal phenotype and extraction socket healing

The healing characteristics of the extraction socket are complex and are directly influenced by the structural composition and cellular activity of the contiguous bone and mucosal tissues and a cellular regulated response (Gurtner et al., 2008). Dental research has sought to breakdown and classify the periodontal tissue according to several biotypes, categorised by dimensional and observational characteristics, with authors generalising that thick bony plates were associated with thick biotypes and thin bony plates associated with thin biotypes, with each group having a different characterised response to oral surgery (Pontoriero and Carnevale, 2001) periodontal disease or tooth extraction (Kao and Pasquinelli, 2002). It is important to remember that the situation is more complex, with significant individual variability.

The periodontal phenotype is a qualitative classification, representative of the characteristics and morphology of the buccal osseous architecture and gingival complex, the dimensions and topography of which, will have a direct influence on implant outcomes (Kois, 2004, Lee et al., 2011). When considering the anterior maxilla, a thick-scalloped or thick-flat phenotype patient may have a higher chance of retaining the original socket morphology, due to the protection offered by the thicker socket wall and gingival tissue, whilst the thinner bone and gingival thickness of the thin-scalloped patient, may predispose to bone resorption and gingival recession. Knowledge of these risks would be essential when discussing consent with the patient, particularly as the separate attributes may directly influence the treatment planning of the case, the surgical protocol, extent of buccal tissue resorption and the requirement to undertake bone augmentation at implant placement. The gingival phenotype directly impacting on the aesthetic outcomes, peri-implant mucosal stability and patient satisfaction.

The recognition of a thick or thin osseous bone contours, would also influence the risks attributed to fracture of the socket wall, the integrity of the bone in response to infection or post extraction management (Chappuis et al., 2015, Chappuis et al., 2017). If the buccal socket wall was recorded at less than 1mm, there would be a higher change of tissue resorption, affecting implant surgical planning and prosthetic outcomes (Tarnow et al., 1992, Ferrus et al., 2010). The improved modelling and remodelling ability with thick phenotype patients may be attributed to presence of lamellar and bundle on the buccal wall, preventing complete loss of the buccal wall. Alveolar ridge preservation procedures and a gingival graft should be considered in cases with a higher risk of bone resorption and soft tissue dimensional loss, to improve opportunities for future implant treatment.

The characteristics of the thick and thin periodontal phenotypes and their response to intervention are detailed below (Table 4***).***

***Table 4**. Summary of Periodontal Phenotype and its Relationship to Bone and Gingival Tissue Response*

Characteristic Examined	Thin Phenotype 42.3% (Vlachodimou et al., 2021)	Thick Phenotype 51.9%
Response to trauma / disease	Increased risk of gingival recession. Greater risk of recession following invasion of biological width with restorative margins.	Less risk of gingival recession. Greater risk of gingival inflammation following invasion of biological width with restorative margins.
Fixed keratinised Zone	Narrow Zone. (2-4mm)	Increased height of zone. (5-6mm)
Biological width (Dento-gingival width)	0.2 – 3mm	3 – 6.9mm
Gingival Thickness	Less than 2mm	2- 4mm
Gingival Scalloping	High	Flat
Bone scalloping	Pronounced scalloping.	Mainly flat. 15% High scallop
Gingival Recession risk	High	Low
Dehiscence and fenestration risk	Increased	Decreased
Thin Marginal Bone	Thin (less than 1mm)	Thick bone plate (greater than 1mm)
Tooth Form	Tall and tapered teeth. Triangular in shape.	Broad, more apically located contact area. Square anatomic crown.
Response to disease	Increased risk of attachment loss and recession.	More resistant to attachment loss. Formation of deep pockets and infra bony defects.
Response to tooth extraction	Increased risk of soft tissue and bone loss.	Reduced risk of bone and soft tissue loss.
Implant	Thin peri-implant width. Greater risk of vertical gingival and alveolar bone loss following surgery. Higher risk of peri-implant recession and papilla loss.	Thick Peri-implant width. Less risk of vertical gingival and alveolar bone loss following surgery. More resistant to recession and papilla loss.

It is desirable to have a thick periodontal phenotype in an edentulous area, as a more robust bone foundation and thicker gingival tissue can facilitate an improved healing response to implant surgical trauma, reduce the risk of gingival recession (Baldi et al., 1999), increase the vascularity at the healing site and might

suggest the presence of a thick underlying bone foundation for fixture placement (Zweers et al., 2014, Lee et al., 2011). Kennedy (1974) proposed that a thick gingival biotype enhanced the contralateral blood supply to the underlying bone, whilst a thin biotype compromised it. A tendency for more gingival recession was also found with immediate single tooth implant restoration, in a thin scalloped phenotype (Evans & Chen 2008), with a reduced risk of recession in patients with a thick biotype (Cosyn et al. 2011).

After tooth extraction and socket healing, a thicker mucosal layer is also considered beneficial to long-term implant survival, reducing the risk of peri-implant mucositis and improving the aesthetics of the restorative outcome (Berglundh and Lindhe, 1996, Nisapakultorn et al., 2010). Nisapakultorn et al. (2010) and Avila-Ortiz et al. (2020), postulates that the peri-implant phenotype was associated with the facial marginal mucosal level. Patients with a thin phenotype had less papilla fill and had an increased risk of peri-implant facial mucosal recession.

Whilst the mucosal thickness and keratinised dimenions are important, Sapata et al. (2019) demonstrated that the external soft tissue contour was not representative of the underlying bone topography. He reported 30 % soft tissue horizontal expansion at 1 mm, 22% at 3mm, 11.5% at 5 mm and 2% at 7 mm. The soft tissue compensation in the first 3.00 mm was considered the most important, due the local buccal bundle bone loss in this area. Chappuis et al. (2015) also observed that the soft tissue expansion, significantly compensated for underlying bone loss, with no significant correlation found between soft tissue thickness and the underlying facial bone wall thickness (Chappuis et al., 2017, Frost et al., 2015).

Jivraj et al. (2006) stated that the tissue biotype would also have a prominent role in planning the depth and bucco-palatal position of the implant. A thin biotype with highly scalloped tissue may require the operator to place the implant body and shoulder more palatally, to mask the risk of titanium show through (Jung et al., 2007). This change may encourage fixture placement in a suboptimal position, affecting the emergence profile of the final restoration. A thick gingival biotype or peri-implant gingival collar of more that 2-3 mm, was required to mitigate again this effect (Jung et al., 2007, Lee et al., 2011). The advantage of a thick-flat biotype was seen in immediate single-tooth implants cases, where there was a strong correlation between presence of the interproximal papilla and a thick biotype. (Romeo et al. 2008).

Extraction Socket Healing

1.12 Tooth extraction socket healing

Extraction of a tooth is a surgical procedure, which has been described as a tissue amputation leading to functional, psychological, postural and local dimensional changes (Atwood, 1963). The procedure initiates a complex cascade of changes, that promotes healing at the site to re-establish the body's homeostasis. The act of healing and regeneration is commonly referred to as "socket healing".

Extraction of the tooth may be precipitated by carious breakdown of the tooth, periodontal disease, endodontic infection, tooth and bone fracture or local jaw pathology, with these different pathologies causing local tissue loss prior to removal of the tooth (Kingsmill, 1999, O'Brien et al., 1994, Irinakis and Tabesh, 2007). Additional bone and soft tissue damage can occur as a result of the extraction process (Bodic et al., 2005) and during physiological healing at the extraction site (Atwood, 1971, Lekovic et al., 1998). The cumulative effect of these changes is a significant and progressive modelling of the alveolar ridge (Chappuis et al., 2017, Hansson and Halldin, 2012, Sculean et al., 2019). This modelling process causes local changes to the composition of the compact and cancellous bone (Ulm et al., 1992), a reduction in local bone density (Ulm et al., 1992, Reich et al., 2011) and alteration to the height, width and 3D morphology of the site (Schropp et al., 2003b, Araujo and Lindhe, 2005, Bartee, 2001, Atwood, 1971). Although the physical damage caused by extraction of the tooth can be reduced by performing a syndesmotomy procedure (Oghli and Steveling, 2010), sectioning of the tooth or using vertical tooth extraction systems and atraumatic extraction elevators, modelling and subsequent remodelling of the alveolar ridge and gingival tissues is inevitable (Schropp et al., 2003a, Schropp et al., 2003b), as total regeneration of the site does not occur (Kingsmill, 1999).

1.13 Rate of healing

The healing of the extraction socket is a co-ordinate and multi-factorial process and is often reviewed with regards to the individual responses initiated within the gingival and alveolar tissue or discussed within the context of human or animal models.

Remodelling of the oral tissues is a multifactorial process (Pagni et al., 2012), with different rates of healing recorded in separate individuals, at different times in the same individual, in patients with specific facial morphology (Mercier and Lafontant, 1979), at individual tooth positions (Huynh-Ba et al., 2010) and as a result of anatomical (Lindhe et al., 2013), prosthetic (Ozan et al., 2013, Kelly, 1972) and functional factors (Jahangiri et al., 1998, Saunders et al., 1979). The rate of healing in the oral mucosa is also reported as being faster than that of other cutaneous body sites (Szpaderska et al., 2003, Kumar et al., 2013), potentially being due to a reduction in the bodies inflammatory response in the oral environment (Szpaderska and

DiPietro, 2005). Differences in the rate of tissue remodelling and the degree of bone loss are also reported in the mandibular and maxillary arches (Kotze et al., 2014, Atwood and Coy, 1971), with the mandibular alveolar bone demonstrating a higher level of tissue loss following tooth extraction (Johnson, 1969, Tallgren, 1966). This finding is disputed, as Atwood and Coy (1971) and Moya-Villaescusa and Sanchez-Perez (2010) found no difference when analysing radiographs, with Nemcovsky and Serfaty (1996) reporting a reduction rate of 0.4mm per year in the mandible and 0.1mm in the maxilla.

Systemic conditions including diabetes (Nauta et al., 2011), vascular disease, malnutrition (Jahangiri et al., 1998), radiation exposure, immunodeficiency, osteoporosis (Hirai et al., 1993, Bollen et al., 2004), renal disease (Gupta et al., 2015) and endocrine disorders (Malden et al., 2009, Huang et al., 2013) pre-extraction infection (Rutkowski et al., 2007) and the patients age (Kloss and Gassner, 2006) have also been found to alter the healing mechanism and reduce the potential for regeneration of the extraction site. These conditions can alter the physiological and metabolic process of the body (Bartee, 2001), resulting in reduced bone production, less cellular differentiation and reduction in the keratinised mucosa and the gingival architecture.

Habits including smoking have been shown to be implicated in a higher risk of post extraction complications, poor healing and increased functional remodelling of the site. Tobacco is a known peripheral vasoconstrictor, with the nicotine element increasing platelet adhesiveness, the risk of microvascular occlusion, and tissue ischemia. Smoking is also associated with catecholamines release, resulting in vasoconstriction and decreased tissue perfusion. It is believed to suppress the innate and host immune responses, affecting the function of neutrophils (Balaji, 2008).

Flap elevation during surgical removal of the tooth is also a concern (Araujo and Lindhe, 2009, Engler-Hamm et al., 2011, Fickl et al., 2008a, Pfeifer, 1965), with Wood et al. (1972) reporting that a mean loss of 0.23–1.6mm of crestal alveolar bone height occurred, when lifting of a full-thickness muco-periosteal flap. This change was attributed to the surgical trauma inducing an acute inflammatory response, leading to a cell mediated resorption of the exposed bone and socket surface (Brägger et al., 1988, Wood et al., 1972, Yaffe et al., 1994).

1.14 Gingival tissue healing

The healing event at the extraction socket is initiated following removal of the tooth and reprises the process of intramembranous bone formation. The initial surgical trauma results in direct damage to the alveolar bone process and supporting periodontium, rupturing the blood vessels in the periodontal ligament and apical foramen, causing separation of the periosteum and connective tissue attachment. Bacterial

contamination of the site initiates an acute inflammatory response, with release of thromboplastin and factor VII leading to platelet aggregation, primary haemostasis and blood clot formation in the socket (Nauta et al., 2011).

The gingival tissue healing plays an important part in the establishment of a barrier seal against external oral agents at the tooth boundary, through cicatrisation and the re-establishment of the body's homeostasis (Hämmerle et al., 2014). The healing process can either lead to normal repair of the site, defective healing or the formation of scar tissue, with only selective regeneration of elements of the extraction socket (Cohen and Cohen-Lévy, 2014). As tooth extraction is an excisional process because wound edges are not approximated, gingival healing occurs by a secondary intension process. Secondary intent healing requires the formation of a bridge of granulation tissue to close the socket opening before repair of the area occurs. The healing is described in the context of repair, as normal anatomy and function is not restored (Harrison, 1991). The gingival healing process involves four different stages, these include, ***clotting and inflammation, epithelial healing, connective tissue healing and maturation and remodelling***. There is significant overlap of these actions. It is worthwhile examine the first two stages of the inflammatory and epithelial healing response before exploring the modelling, proliferation and maturation of the bone within the alveolus (Sculean et al., 2019). This will enable clarification of the early stabilisation and clots formation stages and prevent duplication when reviewing alveolar bone healing.

1.15 Blood clotting and inflammation

Rupture of the PDL and microvasculature, causes the release of plasma proteins including plasminogen, fibrinogen, fibronectin and albumin. Cell mediated initiators are similarly released, initiating an inflammatory response and the aggregation of platelets, neutrophils and red blood cells. This response results in the formation of an initial blood clot through the intrinsic and extrinsic clotting cascade. Following this phase, a new cellular matrix is formed by continued crosslinking of the fibrin meshwork, with the conglomerate of cells and the fibrin-rich matrix frequently termed the "provisional extracellular matrix". This early fibrin clot seals the wound and provides a structure for cellular movement and reorganisation (Cohen and Cohen-Lévy, 2014).

The fibrin blood clot and the released inflammatory mediators initiates the migration and recruitment of inflammatory cells into the socket site. Neutrophils are attracted by chemotactic agents, the complement system, and by peptides, acting to phagocytose microorganisms and antigenic material in the area. Their number rapidly decrease over 24- 48hrs, when monocytes increase in numbers, with these cells transforming into macrophages. The primarily catabolic inflammatory process is then replaced by an

anabolic phase of connective tissue formation that results from migration of endothelial cells, fibroblasts and the epithelial cells into the area (Martin, 1997). Endothelial cells are derived from peripheral vascular progenitors, with fibroblasts migrating from the connective tissue in the wound edges or originating from monocyte-derived fibrocytes. Epithelial cells are derived from the keratinocytes present at the wound edges (Harrison, 1991).

1.16 Epithelialisation

Epithelialisation of the extraction site is undertaken by division of the basal stratum, starting from cells at the boarder of the wound site. The speed of regeneration is high, with tissue remodelling recorded within 12 hours of the initial trauma. Interleukin-1(Graves et al., 2001, Barhanpurkar et al., 2012) and transforming growth factor (Nauta et al., 2011) are released into the oral tissues and play an important role in this healing process. Their expression and chemotactic activity can vary in individuals (Cohen and Cohen-Lévy, 2014), with these variation accounting for differences in the biological healing profile of patients.

The migrating epithelial cells move as a layer of cells over the fibrin substrate, with the epithelial migration stopping when cellular contact is established from all sides. Once a seal is established, the cells undergo active mitosis to reform the epithelial barrier, allowing the re-establishment of the stratified squamous layering. The continuity of this layer aids in subsequent connective tissue formation, increasing wound strength and limiting the loss of nutrients.

The reformed epithelial layer continues to develop up to day 25- 35 (Amler, 1969, Trombelli et al., 2008), contracting with maturation of the underlying connective tissue and remodelling in response to the functional demands of the site. Although the gingival repair process may be histologically complete after this period, the total remodelling response may occur over a 6-to-12-month period. At the end of healing, the body fails to completely reconstitute the soft tissue architecture of the site (Thoma et al., 2009), with clinical studies indicating a reduction in the gingival papilla height, a narrowing of the fixed keratinised tissue region, reduction in the tissue thickness and volume and apical migration of the crestal gingival margin (Tarnow et al., 1996, Jemt, 1997, Schrott et al., 2009, Darby et al., 2009).

1.17 Bone healing

Extraction socket healing is determined clinically complete, when the socket aperture is sealed, and the alveolus is reconstructed through bony infill and epithelial cicatrisation. The timing of this healing process can be variable (Carlsson and Persson, 1967, Johnson, 1969), with the socket entrance restored between 10

to 20 weeks (Tal, 1999) and radiographic bone fill observed between 3- and 6-months post-extraction (Schropp et al., 2003b).

The healing rate is influenced by the biologic differences between individuals, the size of the alveolar socket and the extent of trauma to the socket margin during the extraction procedure. The ensuing sequence of healing and regeneration is complex and has been described in animal and human studies. Although there is agreement that similarities exist between the histological findings from both groups, the use of the results from animal models to justify the sequence of human healing, should be interpreted with caution, as animals are known to regenerate oral tissues faster (Araujo et al., 2015) and more completely (Steiner et al., 2008).

The initial stage of post extraction socket healing is a bone modelling process, where the external and internal surface of the socket wall undergo dimensional change through the independent action of osteoblast and osteoclasts activity. Bone remodelling involves the removal of mineralized bone by osteoclasts coupled by the formation of bone matrix through the osteoblasts that subsequently become mineralized. The post extraction dimensional change is therefore more the result of modelling rather than remodelling.

1.18 Bone formation and remodelling

Bone formation in the extraction socket is initiated by the development of a blood clot. Rapid fibrinolysis of the coagulum starts within the extraction socket at 2 to 4-days after tooth removal (Cardaropoli and Cardaropoli, 2008). The process results in reorganisation of the provisional matrix, through the formation of a loose connective tissue, with penetration of the site by vascular endothelial tissue and bone forming cells. Early bone formation is initiated by osteoblast cells as early as 2 weeks, through the formation of a dense collagen matrix and a woven structure called “osteoid tissue”. (Cardaropoli et al., 2005). Osteoid tissue then undergoes further mineralisation and maturation, to form woven bone. Woven bone starts to form as finger-like projections, which are laid down around the blood vessels. Eventually, the projections surround a blood vessel, and a primary osteon is formed. The primary osteons may be occasionally reinforced by parallel-fibered bone. Woven bone can be identified within the socket as early as two weeks and at four to six weeks completely fills the defect area (Cardaropoli et al., 2003). Woven bone is a provisional type of bone, without any load-bearing capacity and undergoes further maturation according to the functional demands on the site.

At the periphery, the woven bone starts to remodel into a mature structure, forming lamellar and trabecular bone and internally marrow spaces. The lamellar bone is highly organised, with a parallel alignment of the internal bone fibres. At eight weeks, cortical bone can be seen at the edges of the extraction socket, with

the process of restructuring and reorganisation of the cortical layer ongoing for between 6 to 12 months (Cardaropoli et al., 2003).

1.19 Signalling molecules involved in healing

Several key signalling molecules and regulators are derived from platelet and osteoblast cell lineages to coordinate and modulate cell growth and bone development (Geurs et al., 2014). These molecules include pro-inflammatory cytokine, growth factors and bone morphogenetic proteins and act to influence cellular migration, proliferation and maturation at the extraction socket site. The pro-inflammatory cytokines include: Interlekin-1 and 6 with the regulatory growth factors comprising Platelet-Derived Growth factor (PDGF) (Wallace et al., 2013), Insulin Like Growth Factors (ILGF), Transforming Growth Factor-β (TGF) (Turri et al., 2016) and Fibroblastic Growth Factor (FGF).

Growth factors are signalling molecules that play a role in cell proliferation, migration, and extracellular matrix formation (Darby, 2011, Jamjoom and Cohen, 2015). The growth factors are activated at the early stages of bone healing, initiating cellular division and angiogenic growth (Lalani et al., 2003). Trauma results in an early immunological response, which increases production from the mesodermal derived PDL fibroblasts and endothelial cells (Gao et al., 1996). The FGF growth factor helps to regulate laminin production and angiogenesis, assisting in chemotactic proliferation of fibroblasts and cellular differentiation of pre-osteoblasts (Matsumoto et al., 2012). Vascular endothelial growth factors (VEGF) are released over an extended period during socket healing, aiding in angiogenesis and endothelial growth. PDGF's are released during the first few days of healing, promoting differentiation and migration of specialist mesenchymal cells. They help in the migration of monocytes, macrophages and fibroblasts into the wound site, promoting cell proliferation and chemotaxis. These cells help to accelerate the healing process, through the formation of collagen and an extra cellular matrix (Geurs et al., 2014).

Transforming growth factor is a large family of chemical messengers including TGF-β2 and Bone Morphogenetic Proteins (BMPs) (Urist, 1965), which regulate the action of osteoclasts and osteoblasts. TGF-β2 is associated with the production of the extra cellular matrix and bone formation. Its secretion leads to the enhanced production of collagen and fibronectin and the expansion of osteoblast precursors. BMPs are secreted by perivascular and periosteal osteoprogenitor cells. They act on undifferentiated mesenchymal cells, leading to the development and differentiation of bone matrix secreting cells. They promote the differentiation of stem cells into osteoblasts, leading to enhanced bone formation. A progressive rise of BMP secretion by osteoblasts is seen over a 5 to 10-day period, inducing the production of osteoid matrix and regulating osteoclast function. This secretion phases is then followed by a fall in BMP levels at 14 days,

related to the maturation and mineralisation of the new bone matrix. Trombelli et al. (2008) studied human extraction socket bone healing over a 24-week period, finding that BMP production increased over a 2 to 8-week period, leading to an increase rate of bone modelling and remodelling activity and increased synthesis of woven bone, from the provisional matrix. The interaction between the TGF, BMP and FGF signalling molecules is complex and represents a significant overlap of cellular activities, migration differentiation and maturation (Howell et al., 1997).

1.20 Socket healing in animal models

Socket healing has been investigated in several animal models (Lin et al., 1994, Araujo and Lindhe, 2005, Cardaropoli et al., 2003, Pietrokovski and Massler, 1967, Kuboki et al., 1988, Cardaropoli et al., 2005, Sato and Takeda, 2007, Euler, 1923, Yoshiki and Langeland, 1968, Hsieh et al., 1994, Lekic et al., 2001a, Kanyama et al., 2003, Claflin, 1936). A summary of their findings has been detailed below:

- Euler (1923) examined socket healing in dogs over a 9-week period and outlined a sequence of tissue remodelling changes. He suggested that following coagulation of the blood released from torn vasculature, angioblastic ingrowth occurs at the base and midsection of socket, with coronal epithelium proliferation resulting into coverage of the clot. Fibroblasts subsequently differentiate and migrate into the clot to eliminate fibrin and blood debris. Primary osteoid was produced following maturation and differentiation of mesenchymal cells, with woven bone formed, following osteoblastic activity. Mature lamellar bone re-establishes the continuity of the tissue but at a reduced total bone volume. He proposed that the process could be simplified into the following stages: (1) haemorrhage; (2) coagulation; (3) thrombosis of the vessels of the alveolar wall; (4) organisation of fibrin in the clot; (5) proliferation of the epithelium over the surface of the wound; (6) resorption of the damaged tissue, and (7) formation of new bone.

- Claflin (1936) reported on normal and delayed healing patterns in the dog. He suggested that at 3-days, epithelialisation had started, with osteoblasts present on the bone wall and fibroblasts invading the clot. New bone formation was noted on the base of the socket wall between 5 and 11-days. At 19-days, bone formation reached the crest of the socket, although a central region of clot remained. By 28-days the socket was filled by new bone.

- Pietrokovski and Massler (1967) scrutinised the epithelial healing characteristics and the dynamics of the bone resorption in the mandible and maxilla of the rat, after the extraction of a single or two adjacent teeth. He found that at 1-week, there was a contrast in the histology of the surface connective tissue and the socket area. In the socket, the epithelium had proliferated to cover the wound surface, with the new surface irregular in composition, few rete pegs, a thinner layer of keratinisation and only one thin layer of epithelial cells in active proliferation. The socket was predominately composed of connective tissue with an abundance of collagen fibres arranged parallel to the socket surface. A small number of mature fibroblasts were present in the socket area, with polymorphonuclear leukocytes almost entirely absent. Osteoblastic activity was seen under and on the socket walls, with bone resorption observed on the external surface of the alveolar process. Bone resorption was more pronounced in the mandible in comparison to the maxilla, with this difference attributed to the improved blood supply in this area.

- Yoshiki and Langeland (1968) reviewed the healing of alveolar sockets in monkeys at 1 and 2-weeks after tooth extraction. Tissue specimens were examined to determine the stages of newly formed intramembranous bone, finding osteoid matrix formation within the bone biopsies over this period. Comparison of alkaline phosphatase activity and bone minerals levels demonstrated that extracellular enzyme activity was present both within the new osteoid matrix and in the diffuse calcifying bone matrix.

- Kuboki (1988) studied the activity and biosynthesis of collagen prior to lamellar bone formation in the rabbit. He found that the ratio of dihydroxylysinonorleucine to hydroxylysinonorleucine in the collagen from normal alveolar bone was 4.4. This value increased fourfold, on the 10th day after tooth extraction, coinciding with a phase of woven bone formation and then rapidly decreased towards a normal value on the 14th day. The findings suggest that active biosynthesis and fibrogenesis of bone collagen precedes the completion of lamellar bone formation.

- Hsieh et al. (1994) used fluorochrome bone labels, to identify mineralizing bone surfaces at 5, 10 and 14-days post-extraction in the rats. The mineral apposition rate, mineralizing surface and mineral formation rate were then determined at various locations of the healing socket. A linear decrease in all three measurements was found from gingiva-palatal to gingiva-buccal regions. These differences were related to variations in the vascularity, as the gingiva-palatal region is adjacent to the greater palatine artery.

- Lin (1994) examined the differentiation of periodontal ligament and endosteal fibroblasts into osteoblasts at the extraction site. He noted that proliferation of fibroblasts was low until 16-Hrs after tooth extraction but dramatically increased to a maximum level at the end of 1-day. Between 4 and 5-day, fibroblasts began to differentiate into osteoblasts and form new bone, with the level of residual fibroblasts decreasing to baseline values at 5-days. He concluded that PDL fibroblasts actively proliferated and migrate into the coagulum, forming dense connective tissue. These cells then differentiated into osteoblasts, which formed new bone during socket healing. Endosteal and para-vascular fibroblasts contributed only a small population of fibroblasts to socket healing.

- Lekic et al. (2001b) reviewed the origin of progenitor cells in the healing extraction socket in the rat, examining whether the healing was evoked from cellular proliferation from the periodontal ligament, the tooth or bone surface. The findings of the study indicate that dexamethasone-dependent progenitors were present both on the root and bone-related sides of the periodontal ligament.

- Kanyama et al., (2003) investigated the presence of connective tissue growth factor (CTGF) in rats over a 2 to 14-day period, as CTGF has been found to play an important role in angiogenesis, granulation tissue formation and induction of alveolar bone repair. He observed that in the first 4-days of healing, CTGF was strongly expressed from the endothelial cells migrating into the granulation tissue at the bottom of the sockets. Osteoblast-like cells proliferated into the sockets between 7 to14-days, when CTGF factors were reduced.

- Cardaropoli (2003 and 2005) examined bone formation in an augmented and non-augmented extraction socket, over a 180-day period in the dog. He assessed the gross morphological features of the socket and recorded variations in the mineralisation and provisional matrix levels during healing and detailed whether the site formed a bone bridge or calcified cap. He found that non-augmented sites healed by a hard-tissue bridge, with the central and apical portions of the socket composed of 61% bone marrow and 39% mineralized connective tissue. The tissues present at the extraction site appeared to be more mature than those present in a surgically produced defect of similar dimension. Woven bone was noted to fill most of the socket at 14-days. Osteoclastic remodelling of the woven bone and soft tissue organisation and keratinization was noted at day 30.

- Araújo (2005) reviewing the stages and location of bone loss in the premolar site, in dogs. He observed that marked dimensional changes occurred during the first 8-weeks of healing. Over this

review period, there was a marked osteoclastic activity resulting in resorption of the crestal region of both the buccal and the lingual bone wall. The reduction in the height of the buccal bone was more pronounced than the lingual bone wall of the extraction socket. The height reduction was accompanied by a "horizontal" bone loss that was caused by osteoclasts present in lacunae on the surface of both the buccal and the lingual bone wall. He indicated that resorption of the buccal/lingual walls of the extraction site occurred in two overlapping phases. During phase 1, the bundle bone was resorbed and replaced with woven bone. Since the crest of the buccal bone wall was comprised solely of bundle bone, this modelling resulted in substantial vertical reduction of the buccal crest. Phase 2 included resorption that occurred from the outer surfaces of both bone walls. The reason for this additional bone loss is poorly understood. A lack of complete formation of the edentulous ridge was found with no bone cap to the healed socket.

- Sato and Takeda (2007) evaluated the level of cellular activity in the periosteum, periodontal ligament and trabecular bone during socket healing in the rat. Apoptosis in the tissues peaked at 12-hours, with maximum cellular proliferation seen at 5-days with the start of bone formation. The proliferative activity in the early stages of post extraction wound healing was initially seen in the remaining periodontium, associated with load-induced apoptosis. The next highest's level of activity was associated with proliferation of the fibrous tissue and the formation on new trabeculae bone.

1.21 Human studies

The histology of human extraction-socket healing has been reported on by Mangos (1941), Amler et al. (1960), Amler et al. (1964), Amler (1969), Boyne (1966), Devon and Sloan (2002), Evian et al. (1982) and Trombelli (2008). These authors extracted bone biopsies from healing socket sites and examined the histological changes and bone maturation over a 4 to 16-week period. The findings from these research studies must be interpreted with caution, because the reported observations from Amler et al. (1960, 1969) were over a relatively short observation period, with Devlin and Sloan (2002) using patients diagnosed with systemic illness, whose healing characteristics may not represent that of healthy individuals (Steiner et al., 2008). A summary of the results from human studies are detailed below:

- Amler (1969, 1960, 1964) proposed that following formation of the primary blood clot, granulation tissue was established. After 20-days of tissue remodelling, osteoid bone formation had begun at the base and periphery of the extraction socket and after 6-weeks the socket margins were noted to harboured islands of immature woven bone. All stages of bone regeneration progressed from the

apex and periphery of the socket, towards the centre and crest of the site. Bone fragments from the socket wall were exfoliated into the granulation tissue during healing. Epithelium was found to require between 24 to 35-days to completely cover the extraction socket, enveloping islands of granulation tissue, debris, and bone splinters during its development.

- Boyne (1966) observed that bone formation started at 8 days, beginning from the lamina dura layer and extending onto the socket surface at 10 to 12-days.

- Devon and Sloan (2002) used immunostaining to reveal that at 2 weeks, new areas of woven bone were present at the periphery of the socket, with osteogenic precursors present in this area. The periodontal ligament was observed to be displaced into the healing socket.

- Evian et al. (1982) found that after 4 to 8-weeks of healing, proliferation of cellular precursors had occurred with evidence of connective tissue formation. At 8-weeks, evidence of the presence of woven bone, osteoid tissue and osteoblasts were present within the bone samples. From 8 to 12-weeks, the bone underwent further maturation to form a trabecular pattern, with a reduction in osteoid tissue and fewer osteoblasts noted. By 12 to 16-weeks, the bone in the socket resembled mature alveolar trabecular bone. It was implicated that two phases of bony regeneration were present, the first being from 4 to 8 weeks where proliferation of osteogenic cells results in immature bone formation, with the second phase occurring over the 8 to 12-week period, when osteogenesis slows during the formation of mature trabeculae bone.

- Steiner et al. (2008) agreed with the timings found by Evian et al. (1982) when examining osteoblastic proliferation but proposed that the bone of the original socket wall dies, and that this layer is undermined by osteoclastic resorption. This necrotic bone was then expelled as a Sequestra into the oral cavity or incorporated into the developing socket to be used as a nidus for new bone formation.

- Trombelli et al. (2008) observed that the rate of healing varied markedly between patients but agreed with Amler et al. (1960 and 1969) regarding the stages of early clot formation and the production of granulation tissue over the first 2-4 weeks. He proposed that an intermediate healing phase occurred at 6 to 8-weeks, when osteoclast activity peaked, and the density of vascular structures was high. The provisional matrix was replaced by woven bone during this period, with further modelling of the socket and the formation of new bone slow after this stage. Lamellar bone

was only observed in quantity after 24 weeks, with only 41% of the socket mineralised. The number of osteoclasts cells detected at this point was low, suggestive that remodelling of the bone tissue did not occur until after 6 months.

1.22 Summary of socket healing

The healing and re-organisation of the bone and gingival tissue at the tooth extraction site is complex and multi-factorial. Several distinctive phases of the healing process have been identified in the animal and human models, with the initial trauma leading to clot formation, primary gingival and alveolar remodelling and long-term tissue maturation and development at the site (*Fig. 2*)

Accepting that variations in the timing and cellular activity exist between the animal and human models, an outline of the stages of the healing process could be considered as follow:

a) Tooth extraction and haemorrhage.

b) Coagulation of the clot and thrombosis of the blood vessels. At 12 hours, the clot formation is complete, with the socket filled with blood coagulum, erythrocytes and inflammatory mediators.

c) Angioblastic ingrowth and epithelialization of the socket area starts on day 4 and is associated with the release of CTGF.

d) Fibroblasts proliferate resulting in reorganisation of fibrin within the clot. Mature granulation tissue is formed by the 7^{th} day. Remodelled of the primary blood clot is completed after 7 days.

e) The original socket wall resorbs, with necrotic tissue undermined through osteoclastic activity. The periodontal ligament is displaced into the healing socket between 4 and 6 days.

f) Osteoid bone formation starts at the base of the socket, and under the lamina dura of the side walls at 7 to 8-day. The necrotic bone wall is expelled, with the Sequestra used as a nidus for new growth. Periodontal ligament, endothelial and primary mesenchymal cells provide cellular precursors for osteogenesis.

g) Osteoclastic activity is seen on parts of the socket wall surface after 10 to 12-days, leading to an increase in the synthesis of provisional bone matrix.

h) An abundance of fibrous connective tissue is observed between 13 to 16-days. Rows of osteoblasts are observed in the peripheral osteoid layer, with new bone formation recorded in the lower 1/3 of the alveolus.

i) Replacement of the granulation tissue with newly formed connective tissue is observed by the 20th day.

j) Epithelial proliferation results in complete coverage of the site between 24 to 30-days. The new epithelial layer is presented with reduced thickness and keratinisation and alterations of its rete peg appearance.

k) Initial stage of bone regeneration 4 to 8-weeks. Proliferation of cellular precursors, with a peak of osteoclast numbers and an increase in the number of vascular structures, osteoid tissue and osteoblasts. The provisional matrix starts to be replaced by woven bone, with a loss of the bundle bone causing vertical and horizontal dimensional changes to the buccal and lingual/palatal alveolar process.

l) Second stage of bone formation. Bone maturation occurs, with retardation of osteogenesis between 8 to 12-weeks: Trabeculae of the newly formed bone occupies the majority of the socket. Fewer osteoblasts and less osteoid are present.

m) A dense trabeculae bone is formed at 16 to 24-weeks, with a reduction in the cellular elements within the socket. Very little new bone formation occurs, with few osteoblasts recorded. Lamellar bone is only seen in quantity after 24 weeks.

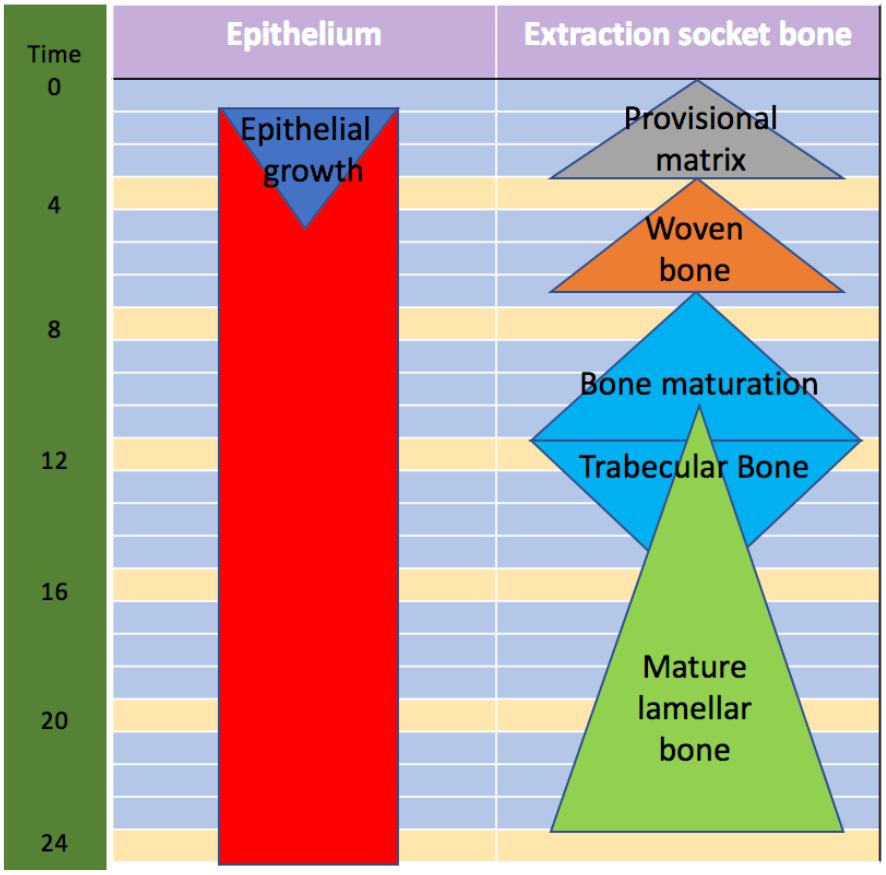
n) Establishment of a healed extraction socket at 6 months. Further progressive remodelling still occurs at the site, with some of the woven bone replaced by lamellar bone. Further changes are dependent on the functional loading and physiological development of the extraction site.

o) Total reconfiguration of the site does not occur, with an enduring change in the vertical and horizontal gingival and alveolar bone dimensions and alteration to the histological characteristics at the site.

p) The residual ridge does not develop a complete cortical layer, with residual changes to the trabecula structure and disruption to the lamellar bone layering.

q) The degree of alveolar remodelling and tissue dimensional change is closely related to the time since tooth extraction in both the maxilla and the mandible.

Figure 2*. Timing of Epithelial and Bone Healing in the Extraction Socket (0- 24 weeks)*



1.23 Histological composition of the extraction socket following healing

The degree of new bone formation and bone modelling at the extraction socket is variable, as differences in the histological composition of the site can vary between individuals and according to the healing period since tooth extraction (Trombelli et al., 2008). Research studies have focused on recording the structure of trephined bone samples (Table 5), detailing the proportion of mineralised bone and connective tissue composition, or reporting on the percentage of lamella or woven bone in the sample (Kingsmill, 1999). The percentage of the mineralised bone found in trephined samples ranged from 25.7% to 54%, with a comparable range of values 43% to 65.5%, recorded for the connective tissue volume.

Lindhe et al. (2013) examined extraction sockets after a minimum of 6 months healing, demonstrating that the relative volume of mineralised bone (lamellar bone + woven bone) was greater in the mandible than in the maxilla (65% vs. 52%) and higher in the anterior part of the mandible (70% anterior vs. 61% posterior). Although both lamellar bone and bone marrow was present in all of the sites, bone marrow was the predominate tissue in the anterior maxilla, whilst dense lamellar bone characterised the anterior portion of

the mandible (62.6% ± 3.2 mandible and 46.1% ± 1.7 maxilla). The newly formed lamellar bone was well organised and concentrically organised at the periphery of the socket site, forming a cortical cap, with the internal bone area characterised by an irregular, finger like extension of trabecular structure. The cortical cap was thicker in the mandible (1.8mm ± 0.2 mm), when compared to the maxilla (0.8 ± 0.1mm), with the thickness of the cortical cap found to be similar in both the anterior and posterior regions of the maxilla (0.7mm ± 0.1 verses 0.9mm ± 0.1). The healed maxillary alveolar ridge contained 22.6 % ± 2.3 bone marrow, with only 16.1% ± 1.5 recorded in the mandible. The proportions of fibrous tissue and woven bone was greater in the maxilla, with the amount of osteoid tissue greater in the mandible.

Carmagnola et al. (2003) examined bone healing over a similar period as Lindhe (2013), demonstrating a lower percentage of mineralised bone (43.5%). This lower value may have resulted from combining the analysis of edentulous sites in both the mandible and maxilla. Aimetti et al. (2009) investigated whether the percentage of mineralised bone differed at different heights within the healed extraction socket, indicating a progressive increase in lamellar bone and a decrease in woven bone, towards the apical region of the socket. This finding may initially suggest support for the bone mineralisation characteristics described by Lindhe et al. (2013). However, as the alveolar ridge in anterior maxilla is thin, the bone sample may have included an increase in the amount of cortical bone in the sample, influencing the histological findings.

Table 5. *Mean Percentage (%) Bone and Connective Tissue Composition Following Socket Healing (Time period recorded in months -m).*

Author	% Total Bone	% Connective tissue	Time period
(Aimetti et al., 2009)	47.2% ± 7.7	65.5% ±25. 85	3m
(Barone et al., 2008)	25.7% ± 9.5	59.1% ± 10.4	7 m
(Cardaropoli et al., 2012)	43.82% ± 12.23	56.17%	4m
(Carmagnola et al., 2003)	43.5%	43%	>9m
(Froum et al., 2002b)	32.4% ±6	51.6% ±36.1	
(Guarnieri et al., 2004)	<46%		3m
(Heberer et al., 2011)	44.21% ±24.88	55.78%	3m
(Iasella et al., 2003)	54% ±12	46%	4-6m
(Pelegrine et al., 2010)	45.47% ±7.21	65.50% ±25.85	6m
(Serino et al., 2003)	48.8% ±14.4	51.16% ±14. 43	3m

Although a variation in the histological composition of the healed alveolar process was observed, what was uncertain was whether variations in bone composition were caused by functional or biological risk factors. A higher level of bone resorption has been suggested following denture loading in the less structurally dense maxilla (Pietrokovski and Massler, 1967). This observation led Maruo et al. (2010) to suggest that

reducing the loading stress from a denture base, would lead to a reduction in the rate of tissue loss (Devlin and Ferguson, 1991). Tallgren (1972) refuted this finding, reporting tissue loss in patients with poorly fitting dentures without a direct tissue contact.

Post Extraction Alveolus Healing Dimensions

1.24 Socket healing and tissue remodelling

Socket healing and post extraction bone remodelling is a slow process (Trombelli et al., 2008) leading to qualitative and quantitative changes to the bone and soft tissue architecture (Cardaropoli et al., 2003, Araujo et al., 2015) as incomplete regeneration of the site never occurs (Amler, 1969, Atwood, 1963). The pattern and the extent of the remodelling effects can vary according to the extraction of single or multiple teeth, leading to distinct differences in the extent of vertical and horizontal tissue reduction (Iasella et al., 2003).

Animal experiments have demonstrated that a significant level of bone remodelling occurred during the first 2–3 months following tooth extraction (Cardaropoli et al., 2003, Cardaropoli et al., 2005, Araujo and Lindhe, 2009), where most of the bundle bone was replaced with newly formed woven bone. Human studies after single-tooth extraction, indicated that the majority of the tissue remodelling process occurred in the first 3 to 6 months of healing (Tallgren, 1972, Pietrokovski and Massler, 1967, Schropp et al., 2003b, Lam, 1960, Moya-Villaescusa and Sanchez-Perez, 2010, Tan et al., 2012), although further transformation and diminution of the ridge can occur (Iasella et al., 2003, Barone et al., 2008). The tissue restructuring results in an edentulous ridge that is thinner and shorter in dimension (Schropp et al., 2003b, Blanco et al., 2011, Araujo and Lindhe, 2009), with a lingual or palatal displacement of the alveolar crest (Bergman and Carlsson, 1985). The resultant ridge morphology has a reduced vertical and horizontal proportion, with a tendency for greater resorption of the buccal than palatal/ lingual bone (Schropp et al., 2003a, Pietrokovski and Massler, 1967, Trombelli et al., 2008, Araujo and Lindhe, 2005).

Additional long-term remodelling effects have been observed by several authors (Iasella et al., 2003, Barone et al., 2008, Brehm and Abadi, 1980, Carlsson and Persson, 1967), resulting in further diminution of the alveolar ridge dimensions (Tallgren, 1972, Reich et al., 2011, Johnson, 1969). The scale of this subsequent change has been found to be variable (Brehm and Abadi, 1980) and slower than the initial “de novo” bone healing (Schropp et al., 2003b). Longitudinal studies indicated that the modelling process is continuous and can be observed over a 25 year period (Brehm and Abadi, 1980). Ashman (2000) reported a yearly bone loss of 0.25 to 0.5% in the mandible, while Kreisler (2003) indicated a dimensional change of 2-7% in the maxilla when examined over an 8-year period. Although some researchers have suggested that the maxilla suffers less resorption than the mandible (Tallgren, 1966, Kalk and de Baat, 1989), these studies were undertaken in fully edentulous arches and cannot be extrapolated into the dentate individual.

The extent (Atwood, 1971, Lekovic et al., 1998, Araujo et al., 2015) and timing (Schneider, 1999, Farina et al., 2011, Pietrokovski and Massler, 1967) of the vertical and horizontal soft and hard tissues changes at the extraction site, has raised concerns regarding the feasibility and outcome of subsequent prosthetic treatment in the edentulous area (Chappuis et al., 2017). This concern is associated with the extent of the dimensional changes and their influence on an operator’s ability to provide a viable, functional and aesthetic

replacement for the extracted tooth. The impact and significance of this dimensional change has been described with regards to prosthetic replacement with a denture (Tallgren, 1966, Watt and Likeman, 1974), a fixed bridge (Atwood and Coy, 1971) or an implant supported restoration (Schropp et al., 2003b, Araujo et al., 2015, Chappuis et al., 2017).

As the averaged width of the anterior maxillary extraction site has reduced to 5.9 mm (2.7–12.2 mm) following 12 months healing, many edentulous sites would require additional grafting to allow optimal positioning of an implant fixture (Mecall and Rosenfeld, 1991, John et al., 2007), whilst avoiding adjacent anatomy (Demircan and Demircan, 2015). The risks associated with this dimensional change are particularly relevant to the anterior part of the maxilla, due to the presence of a thin buccal bone plate, which consists mainly of bundle bone (Araujo et al., 2015).

1.25 Extraction socket dimensional changes following tooth extraction

When a tooth is removed, an extraction socket wall or alveolus remains (*Fig. 3*), with the anatomical structure having a separate buccal/facial, lingual/palatal, and interproximal bone wall. Due to the complexity of the roots anatomical structure, and the different rates of modelling and remodelling in the healing process (Rojo-Sanchis et al., 2021, Araujo et al., 2015), the dimensional changes which affects the extraction socket, and the alveolar process can be difficult. Particularly, as there is no anatomical distinction between the alveolar and the basal bone. This measurement is compounded by the fact that the base of the alveolar process is normally taken as the root apex, but this landmark is lost following extraction of the tooth (Brash, 1928).

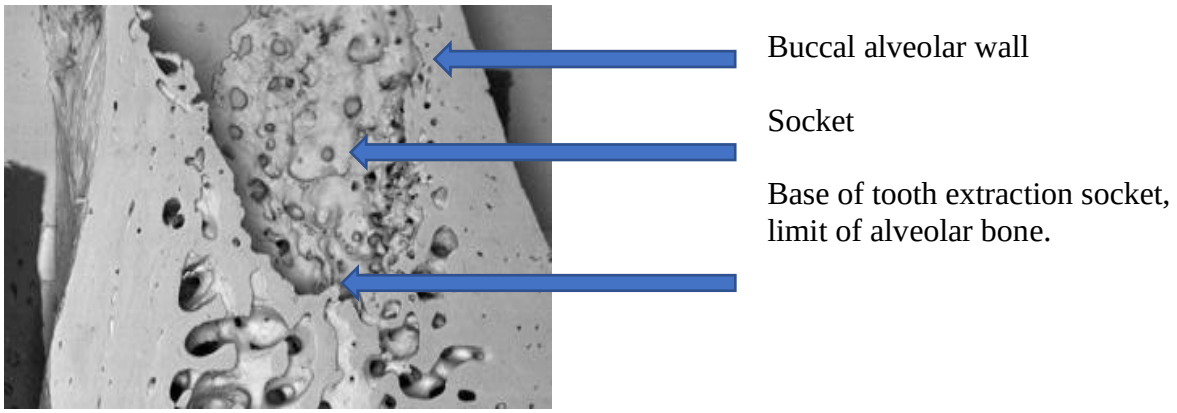


Figure. 3. *Electron microscopy image of the extraction socket and the base of the alveolar bone*

The term residual ridge resorption has therefore been used by authors, to delineate between the dimensional changes in the bundle bone and the alveolar process, rather than the basal bone (Edwards, 1954). To help in describing and quantify these dimensional changes, common reference anatomical positions have been proposed. The measurement and reference positions most described, are the horizontal and vertical alveolar ridge dimensional change, mostly in the mid-buccal and mid-palatal areas and dimensional changes to the interproximal papilla, gingival phenotype and bone morphotype/morphology.

The size of the alveolar dimensional change has historically been examined through unquantified visual analysis (Baker et al., 1979, Jensen and Sindet-Pedersen, 1991), lateral cephalometric radiographs (Carlsson and Persson, 1967), measurement of the bone and soft tissue using callipers (Chen and Buser, 2009, Barboza, 1999), direct re-entry (Iasella et al., 2003), bone mapping (Chen et al., 2008, Wilson, 1989, Barboza, 1999, Salyer and Hall, 1989), comparison of alveolar ridge dimensions from study casts (Pietrokovski and Massler, 1967, Johnson, 1969, Schropp et al., 2003a), intra socket measurements (Lekovic et al., 1997), dimensions from fixed implants (von Arx et al., 1998) and radiographic stents/overlays (Rasperini et al., 2010).

Whether individually or in combination, several newer innovative techniques have been utilised to evaluate the chronology of the resorption process. These include subtraction radiography (Schropp et al., 2003a) and 3D analysis systems (Danforth et al., 2003). The 3D analysis systems include photogrammetric measurements (Lie and Jemt, 1994, Henriksson and Jemt, 2004), the Moire´ projection technique (Studer et al., 1997, Studer et al., 2000), stereometric microscope techniques (Adams and Wilding, 1988), ultrasound or sonography systems (Traxler et al., 1992), CBCT images (Moya-Villaescusa and Sanchez-Perez, 2010, Ziegler et al., 2002), combined optical and CBCT images (Jonker et al., 2021) and magnetic resonance scans.

Radiographs: Although radiographs are the most common form of analysis, the use of conventional intra and extra-oral images for evaluation purposes has its limitations, due to the 2D nature of the image, a reduction in the data set, the requirement for uniformed projection and the need for a radiographic exposure of the patient. Visual interpretation and photographic systems are also prone to error based on the subjective nature of the measurement and the reduced inter operator reproducibility. Calliper and direct bone measurements have been found to be very accurate and reproducible, but when they involve bone sounding, are an invasive technique and can only be undertaken when local anaesthetic has been delivered, or when surgical procedures are being undertaken. Chen et al. (2008) compared the bucco-lingual ridge width using ridge-mapping versus direct calliper measurements, showing that both systems had a variation rate of < 11% when examining for a ± 1 mm deviation between examiners. Less invasive combinations methods

have now been proposed (Oghli and Steveling, 2010, Schropp et al., 2003a), where researchers have examined the combined gingival and alveolar tissue changes in dental casts. Whilst these techniques are simpler, they fail to clarify if the dimensional changes are as resultant of alteration from the mucosal tissue volume, or the alveolar bone.

Projection Systems: The Moire´ shadow or projection systems were developed as a less invasive method of 3D analysis, producing an accurate and reproducible method of assessment. The system is however complex and requires specialist equipment and expertise from the clinician or researcher. It has now been superseded by laser and optical 3D digital scanning techniques.

CBTC Imaging: 3D radiographic imaging, using CBCT was first introduced in 1998 (Mozzo et al., 1998) and has become an established diagnostic technique in dentistry. Whilst expense and radiation dose was originally a limiting factor (Proussaefs et al., 2002, Chen et al., 2008), their development and utility has now made them a mainstay of dental treatment planning (Akyalcin et al., 2013, Amid et al., 2017, Lin et al., 2018). CBCT and occasionally CT images, are now gaining popularity in the measurement of the alveolar process. They have the advantage of collating a greater number of 3D data sets for patient analysis and allow for the use of a flexible voxel-based image system (Bornstein et al., 2017), to aid diagnosis and visual simulations (Fokas et al., 2018).

Whilst CBCT images are considered highly accurate and reliable for linear and area measurements, their accuracy can be affected by several factors (Pinsky et al., 2006). These include the image quality, radiation exposure (kV, mA, and the number of basis images), the software used for image reconstruction and dimensional measurement, patient motion artifacts, and the limitations of the clinician in interpretation (Nikneshan et al., 2014, Fokas et al., 2018).

The development of newer CBCT systems has now increased their versatility and image accuracy, resulting in them now being seen as the preferred method to evaluate bone dimensional changes during tissue healing (Ballrick et al., 2008, Chen et al., 2008, Chappuis et al., 2013).

1.26 Mid-buccal vertical alveolar dimensional change

Changes in vertical alveolar ridge dimensions have been reported on in both human and animal studies, with a greater rate of buccal bone resorption found in the dog (Araujo et al., 2005), rat (Pietrokovski and Massler, 1967) and human models (Schropp et al., 2003b) (Table 6).

When CBCT analysis was undertaken on 14 patients who had undergone single tooth extraction in the incisor, canine and premolar regions, Araújo (2015) found that over a 4 month healing period, the buccal alveolar bone wall was reduced in height by an average of 35%, with the palatal wall suffering a reduction of just 13%. Additional tissue resorption was recorded with continued healing. Greater height reduction was found in the anterior incisor region (-4.9mm ± 3.1), when compared to premolar sites (-3.1 ± 3.2mm). Misawa (2016) found similar results, when comparing CBCT measurements of the alveolar ridge dimensions in the anterior maxilla, over 1 year of healing.

Table 6. *Mean Vertical Alveolar Crest Dimensional Changes Following Tooth Extraction (mm)*

Author	Vertical (mid-buccal) (mm)
(Aimetti et al., 2009)	-1.2 mm ± 0.6
(Barone et al., 2008)	-3.6 mm ± 1.5
(Barone et al., 2013a)	-2.1 mm ± 0.6
(Camargo et al., 2000)	-1.0 mm ± 2.25
(Cardaropoli et al., 2014)	-1.67 mm ± 0.43
(Festa et al., 2013)	-3.1 mm ± 1.3
(Fiorellini et al., 2005)	-1.2 mm ± 1.2
(Iasella et al., 2003)	-0.9 mm ± 1.6
(Lekovic et al., 1997)	-1.2 mm ± 0.13
(Lekovic et al., 1998)	-1.5 mm ± 0.26
(Nevins et al., 2006)	-5.2 mm ± 3.72
(Rasperini et al., 2010)	-2.2 mm
(Serino et al., 2003)	-0.8mm ± 1.6

The difference in the buccal and palatal alveolar vertical bone height was compared by Iasella et al., (2003), Barone et al., (2008), Kerr (2008) and Aimetti et al., (2009). Three of the studies (Iasella et al., 2003, Barone et al., 2008, Aimetti et al., 2009) recorded greater vertical buccal bone resorption, with a vertical change of -0.9mm to –3.6mm, after 3 to 7 months healing. The palatal change was -0.4mm to -3mm. Kerr (2008) found that greater change occurred on the lingual aspect (-1.12mm ± 0.98), when compared to the buccal aspect (-0.95mm ± 1.34), however the buccal measurements had a greater standard deviation, indicating a potentially larger size variability.

Schropp et al., (2003a) indicated that the buccal level of bone generated within the extraction socket never reached the level at the proximal surfaces, with the morphology of the buccal alveolar crest curved, with the lowest point in the mid-buccal surface located 1.2mm apical to the mesial and distal bone crests. Moya-Villaescusa and Sanchez-Perez (2010) noted that the mesio-distal distance between the remaining adjacent teeth, did not affected the degree of vertical bone loss at the buccal site, with the most apical point of the vertical resorption located at 4.32mm (3.85mm to 4.78mm) from the proximal alveolar bone margin.

Nevins et al. (2006) reported even greater buccal vertical alveolar bone loss (-5.2mm ± 3.72) when he examined teeth with prominent roots in the anterior maxilla. This additional bone loss may be attributed to the buccal bone having a thin cortical structure, which was knife-edged in shape and had a greater risk of dehiscence or fenestrations of the socket wall prior to tooth removal. These anatomical characteristics may lead to an increased risk of post-extraction alveolar ridge height reduction. The propensity for increased buccal resorption in comparison to that in palatal or lingual aspect of the socket may also be linked to the anatomic characteristics of the bundle bone in the buccal site, as described by Araújo and Lindhe (2005). Araújo and Lindhe (2005) indicated that a larger proportion of the buccal socket wall was made up of bundle bone. As this bone relies on the periodontal ligament for its blood supply, rather that the intra-alveolar vasculature, it is resorbed during the initial stages of bone healing (Araujo et al., 2008). This early resorption pattern leads to an unequal rate of bone modelling and a greater vertical bone loss on the buccal aspect of the socket (Ferrus et al., 2010, Spinato et al., 2014, Tonetti et al., 2019).

The systematic review undertaken by Tan et al., (2012) observed that an average vertical buccal alveolar bone loss of 11–22% occurred at 6 months healing, with a weighted mean reduction of -1.24mm (-0.8mm to -1.5 mm). The buccal alveolar bone generally displayed more resorption than the palatal aspect, with a rapid reduction in the first 3 to 6 months, followed by a more gradual change. The systematic review undertaken by Van Der Weijden et al. (2009) also indicated a difference in the resorption rates of the buccal and lingual alveolar bone, when a waited mean of - 2.59mm ± 1.85 buccal reduction and -2.03mm ± 1.78 lingual reduction. The vertical resorption levels in these systematic reviews are significantly smaller than the findings of other individual studies (Araujo and Lindhe, 2005), but this difference may be accounted for, as the systematic reviews included a greater number of molar teeth in the analysis, with gender, systemic factors, smoking status and reason for extraction acting to affect the results.

Thin wall bone biotypes in the incisor and canine area demonstrated more advanced bone resorption, when compared to thicker phenotypes in the premolar area (Chappuis et al., 2017), suggesting different socket resorption patterns for the dentition. Sapata et al. (2019) highlighted from CBCT comparative studies, that buccal bone loss mainly occurred at the coronal 3mm, with complete loss of the bundle bone occurring with thin bone phenotypes. This finding was in conformance with the studies by Araújo et al. (2015), Jung et al. (2013b), Llanos et al. (2019), who indicate that the assessment of the facial bone wall thickness provides the clinician with a prognostic tool to estimate the degree of future bone loss prior to tooth extraction (Chappuis et al., 2017).

Post-extraction bone modelling in single-tooth maxillary site, appears to be concentrated in the mid-buccal aspect of the socket wall at 8 weeks post-extraction, while proximal areas suffer less dimensional change due to the blood supply from the periodontal ligament (PDL) of the neighbouring teeth (Chappuis et al.,

2017, Chen et al., 2009). Chappuis et al. (2017) proposed that early bone loss in a thin bone morphotype, resulted in a two-wall defect morphology, whilst an intact thick facial bone wall morphotype produces a three-wall morphology. Both configurations are seen to have high regenerative potential (Schenk et al., 1994). Socket healing studies indicate a decrease in osteoclastic activity at 8-week, suggesting that implant placement should be delayed until after this cellular change in thin phenotype bone patients. This delay would maximise the potential for concurrent osteoblastic activity, promoting healing of the site (Vignoletti et al., 2014).

1.27 Proximal Vertical Changes

A decrease in the amount of vertical alveolar bone height resorption has been reported at the proximal aspects of the extraction socket, when the site is compared to the resorption pattern in the mid-buccal position. The differences observed in the proximal changes are summarised in Table 7. These reports indicate a variation in proximal reduction of between -0.4mm to -1mm.

***Table** 7. Mean Proximal Alveolar Bone Loss Adjacent to the Extraction Socket Site (mm)*

Author	Proximal (Mesial / Distal)
(Aimetti et al., 2009)	-0.5 mm ± 0.2
(Barone et al., 2008)	-0.4 mm ± 1.2 M / -0.4 mm ± 0.8 D
(Barone et al., 2013a)	-1.0 mm ± 0.7
(Festa et al., 2013)	-0.4 mm ± 1.2
(Iasella et al., 2003)	-1.0 mm ± 0.8
(Lekovic et al., 1997)	-1.0 mm± 0 and -1.66 mm ± 0.3
(Saldanha et al., 2006)	-0.93mm
(Serino et al., 2003)	-0.6mm ± 1 and -0.8 mm ± 1.5
Legend: M – Mesial / D - Distal	

Lekovic (1997) and Barone (2013a) reported a reduction of -1mm ± 0.7 in the proximal areas, which was of a magnitude of 0.5mm to 1.1mm smaller than the mid-buccal vertical dimensional changes. However, Barone et al. (2008) and Aimetti et al. (2009) observed a smaller proximal height loss of between -0.4mm to -0.5 mm at 3-7 months healing, but a higher level of mid-buccal loss of -0.9 mm to -3.6 mm. Serino et al., (2003) detected a proximal vertical change of -0.6mm, but found only minor differences between the proximal and mid-buccal measurements (-0.6mm ± 1 and -0.8mm ± 1.5).

Tan et al., (2012) undertook a systematic review of the alveolar vertical bone changes at both the mid-buccal and proximal socket positions. Meta-analysis indicated a weighted mean mid-buccal bone reduction of -1.24mm after 3 to 7 months healing, with only a -0.8mm to -0.84 mm proximal reduction. It was suggested that the difference in the severity of the bone loss, was attributed to the proximal bone retaining a viable blood supply from the adjacent dentition and periodontium (Chappuis et al., 2017, Sculean et al., 2014). The additional vasculature helping to stabilise the interproximal bone and reducing the risk of resorption to 11% from the 22% determined for the mid-buccal position.

1.28 Horizontal alveolar ridge dimensional change

Resorption of the buccal bone at the extraction socket is commonly seen after tooth extraction, with a wide variation in bone resorption patterns recorded (Table 8). These observations revealed that the original contour of the alveolar ridge was never preserved, with a minimal horizontal bone reduction of -2.46mm (Pellegrini et al., 2014) and a maximum of -4.56mm (Lekovic et al., 1998) recorded. The degree of horizontal dimensional change was often considered to be separate to that of the vertical change, but the two measurements are directly interlinked. Vertical crestal resorption can occur as a direct result of damage to the extraction socket wall, or due to osteoclastic activity on the inner and outer socket wall (Araujo and Lindhe, 2005), with the complex pattern of resorption leading to an associated horizontal dimensional change. This association was confirmed by Araújo (2015) and Chappuis et al. (2017), who indicated that the risk of alveolar ridge resorption in the horizontal plane was increased when the buccal bone plate was thin in cross-section, leading to a horizontal dimensional change of 25% over a 4 month period.

Misawa (2016) found a slightly larger horizontal dimensional change of -34.1mm^2 ±20.5 (34%), when using CBCT measurements to calculate the cross-sectional alveolar process changes in the anterior maxilla. The investigators also undertook additional measurements at positions 3mm, 5mm and 7mm apical to the pre-extraction CEJ position. The results indicated a -5.7mm ±2.5, -4.8mm ±2.8 and -3.2mm ±2.7 horizontal change on the buccal bone surface. These measurements equated to a 62% horizontal ridge reduction at the 3mm level, a 46 % reduction at 5mm and a 34% reduction at 7mm. Kerr et al. (2008) noted similar horizontal dimensional changes, when undertaking ultrasound measurements, with Schropp et al., (2003) also demonstrated significant post-extraction changes, including a 50% ridge width reduction within the first 3 months of healing. He also concluded that the horizontal dimensional changes were predominantly due to remodelling of the buccal socket wall.

***Table 8**. Mean Horizontal Alveolar Bone Loss at The Extraction Site (mm)*

Author	Width Change
(Aimetti et al., 2009)	3.2mm ± 1.8
(Barone et al., 2008)	4.3mm ± 0.8
(Barone et al., 2013a)	3.6mm ± 0.72
(Carmagnola et al., 2003)	3.06mm ± 2.41
(Cardaropoli et al., 2014)	4.04mm ± 0.09
(Cardaropoli et al., 2014)	3.06mm ± 2.41
(Iasella et al., 2003)	2.56mm ± 2.3
(Jung et al., 2013b)	3.3mm (43%)
(Fiorellini et al., 2005)	3.7mm± 1.2
(Lekovic et al., 1997)	2.6mm ± 2.3
(Lekovic et al., 1998)	4.4mm ± 0.61
(Lekovic et al., 1998)	4.56mm ± 0.33
(Llanos et al., 2019)	1.6mm ±0.82
(Pellegrini et al., 2014)	2.46mm
Width changes are representative of the contour reduction (mm)	

Ten Heggeler et al. (2011), Van der Weijden et al. (2009), Darby et al. (2009) and Tan et al. (2012) have all undertake systematic reviews, examining the horizontal alveolar ridge dimensional changes following tooth extraction. The results from their meta-analysis demonstrated a very similar outcome, indicating an average width reduction of -3.87mm with a range 2.6mm to -4.6mm. Tan et al. (2012) indicated a horizontal dimensional change of 32% change at 3 months, and a 29-63% change at 6 months. These systematic reviews indicated that several clinical factors have been recognised as having the ability to influence the pattern of horizontal ridge resorption. These include infection at the site, host factors, bone morphology, the size of the socket and the horizontal bone loss prior to tooth removal (Tsigarida et al., 2020). Other influencing factors include sex, age and geographical diversity (Rojo-Sanchis et al., 2021). It was also proposed that a larger socket size required more time to effect bone infill in the alveolus, with a smaller socket requiring less bone infill (Darby et al., 2009).

Critically, horizontal buccal bone resorption has been shown to reach as much as 56% while lingual bone resorption has been reported to be up to 30% (Schropp et al. 2003). A thin buccal bone morphotype was the highest risk factor for horizontal dimensional change (Chappuis et al., 2017, Borges et al., 2020).

Alveolar Ridge Preservation (ARP)

1.29 Alveolar ridge preservation definition

Augmentation protocols have been developed to meeting the increasing demands of clinicians, who require retention of the bone and soft tissue contour of the healed extraction site, to effect successful prosthetic reconstruction (Horváth et al., 2013). These augmentation procedures have been described using the terms: socket augmentation, socket preservation, ridge preservation or alveolar ridge preservation. The intension to "*preserve*" the ridge, does not mean that the original alveolus dimension would be maintained, instead, it relates to the continuance of the bone and gingival tissue contour that was present prior to the loss of the tooth and optimal regeneration of the socket defect (Araújo et al., 2015).

Alveolar Socket Preservation *(ASP*) and ***Alveolar Ridge Preservation*** *(ARP*) are considered the preferred terms for this procedure, with Willenbacher et al. (2016) suggesting that the term ASP should only be used for techniques in which a completely contained extraction socket is filled with a bone substitute material or sealed with a membrane. ARP procedures include augmentation of extraction sockets, with and without minor damage to the socket walls and it is because of this utility, that this term is used in this review.

ARP was defined by Darby et al. (2008) as:

"*Any procedure undertaken at the time of or following an extraction, that is designed to minimise external resorption of the ridge and maximise bone formation within the socket*".

ARP was first described as a method to prevent socket wall collapse in denture patients, with clinicians using acrylic bone cement (Ashman and Bruins, 1985), durapitite (Greenstein et al., 1985, Balshi, 1987) and hydroxyapatite (Quinn and Kent, 1984, Quinn et al., 1985) to minimise the dimensional changes during healing. The procedure has now evolved, as the popularity of implant treatment has increased, to include the use of a combination of cellular and tissue growth factors, synthetic bone substitutes, xenografts, allografts and autogenous bone and soft tissue substitutes (de Carvalho and Okamoto, 1979, Wang et al., 2004, De Risi et al., 2015). The use of innovative techniques, such as ultrasound, have also been proposed as a method to limit dimensional change (Kerr et al., 2008).

1.30 Rational for ARP

The Osteology Consensus Report by Hammerle et al. (2012b) stated that the indications for ARP included:

"*The maintenance of the existing soft and hard tissue envelope, maintenance of a stable ridge volume for optimising functional and aesthetic outcomes and simplification of treatment procedures subsequent to ridge preservation*".

Other clinical indications include sites where the buccal plate is less than 1.5mm to 2 mm thick (Araujo and Lindhe, 2005, Cardaropoli et al., 2014, Chappuis et al., 2015), sites where maintaining bone volume is crucial to minimize the risk of damage to anatomical structures (Leblebicioglu et al., 2007). This includes sites such as the maxillary sinus or inferior alveolar nerve, patients with high aesthetic demands including a high lip line, or a thin phenotype and patients where multiple teeth are to be extracted and preservation of the bone is considered important for long-term prosthetic reconstruction (Jonker et al., 2021).

The use of ARP is limited to exodontia sites without acute infection and where the original socket architecture remains intact (Al-Hezaimi et al., 2011). Although procedures to manage the loss of a socket wall, or the presence of extensive labial or buccal dehiscence defects have been proposed (Elian et al., 2007), these techniques should be considered as a "***Socket Repair Technique***" (SRT). This is because their purpose is to replace the previously lost bone support, reconstructing the three-dimensional alveolar volume for implant placement. ARP promotes healing and maintenance of the existing architecture and not the structural reconstruction of the site (Bartee, 2005, Bartee, 2001). There is potential for an overlap in both treatment modalities, if only a small segment of the bone wall is missing or a dehiscence or fenestration is present, but the adjacent bone architecture should maintain the outline of the socket wall in ARP, without the risk of immediate tissue collapse at the site (Araújo et al., 2012).

Bartee (2001) proposed 3 categories of ARP material, based on the resorption pattern of the graft material that was employed, discussing short, transitional and long-term ARP techniques, although this classification is not used routinely.

Alveolar Ridge Preservation Techniques

1.31 ARP Methods

ARP acts to facilitate physiologically repair and cellular regeneration at the extraction socket, ensuring a stable bone and mucosal tissue foundation prior to prosthetic reconstruction or implant placement (Avila-Ortiz et al., 2019, Tonetti et al., 2019). When considering the characteristics of the ARP materials, it is preferable for the graft to be biocompatible, resorbable, non-antigenic, non-carcinogenic, inexpensive and pose no risk of disease transmission (Jamjoom and Cohen, 2015). The graft material should act as a scaffold to maintain the socket space, whilst operating as a mineral reservoir which promotes the induction of new bone formation (Kumar et al., 2013). Ideally, the graft should have a similar particle size and histological characteristic to that of human bone, with the healing process not adversely affected by the presence of the matrix. It should stimulate complete histological regeneration of the alveolar tissue, ensuring that the new bone structure does not adversely affect the ability to place an implant fixture or alter its immediate and long-term survival characteristics (Jamjoom and Cohen, 2015, Darby et al., 2008, Shue et al., 2012).

Several transitional ARP techniques have been proposed (Horváth et al., 2013, Darby et al., 2008, Wang et al., 2004). Although the different ARP techniques advocate specific clinical approaches, they have several key requirements, including; removal of the tooth using a minimally traumatic process, biocompatibility of the graft material, access to an adequate blood supply, the ability of the graft matrix to provide mechanical support, the capability to function as a barrier to cellular invasion and the availability of odontogenic cells derived from the local host site, or from the implanted graft matrix, to promote new bone formation (Darby, 2011, Bartee, 2001).

1.31.1 Minimally traumatic extraction techniques

To minimise the level of damage during the tooth extraction, several protocols have been developed. Initially, a sulcular incision is undertaken to separate the gingival attachment apparatus around the tooth. This incision reduces the amount of soft tissue trauma and helps to prevent recession of the gingival margin. Extraction of the tooth is then achieved using a minimally traumatic technique, designed to decrease the risk of direct damage to the socket wall (Wang et al., 2004). The procedure may involve the removal of the tooth using forceps, elevators, periotomes and a syndesmotomy procedure. Sectioning of the tooth or local reduction of the lamina dura can be undertaken using a bur or ultrasonic instrument, with careful consideration given to maintaining the integrity of the socket wall (Barone et al., 2013c).

Debridement of the socket wall can be considered, as it will facilitate removal of chronically inflamed tissue and foreign body material, that may act to interfere with healing. There is no direct requirement to perforate the socket wall to promote healing, although some studies (Darby et al., 2008, Buser et al., 1993) have

advocated puncturing the lamina dura with a small bur, to encourage endothelial blood vessel ingrowth, greater blood infill and an improved blood perfusion of the graft material (Buser et al., 1993). Conversely, it has been shown that retention of the periodontal ligament on the socket wall may be beneficial, as its presence facilitates retention of the clot during the early stages of wound healing (Cardaropoli et al., 2003).

1.31.2 ARP surgical protocols

ARP can be undertaken using a graft matrix or barrier membrane alone, or as combination technique, which includes a barrier membrane or matrix and a bone graft material. The graft material can be combined with other bio-scaffolds, growth factors and cellular agents to promote osteogenesis and osteoid deposition (Giannoudis et al., 2005, Laurencin et al., 2006).

The ARP techniques can broadly be divided into three main categories:

- Socket grafts - Using particulate bone grafts or bone substitutes to augment the socket (Adriaens and Van der Stede, 1998, Tan et al., 2012).

- Guided Bone Regeneration (GBR) –Using a membrane alone, or a combination technique with a graft matrix and bone substitute (Adriaens and Van der Stede, 1998, Iasella et al., 2003, Mardas et al., 2010).

- Socket Seal Technique – Using a connective tissue, collagen or alloplast matrix to seal the socket, or a combination technique using a matrix and bone substitute (Lekovic et al., 1998, Bartee, 2001, Jung et al., 2004).

Each ARP technique has a different rational, is associated with alternative surgical protocol and has a different efficacy in being able to preserve the alveolar ridge dimensions or promote bone regeneration in the extraction socket. These techniques will now be considered in detail, outlining the advantages and disadvantages of each material and procedures.

1.32 ARP graft options

After exodontia, and flapless tooth removal, grafting of the site has been recommended as a pre-prosthetic procedure to reduce the risk of tissue loss and promote bone regeneration. It has been advocated to reduce healing times and discomfort for the patient, with placement of a graft material or bio-scaffold, found to inhibit alveolar bone and soft tissue contour loss at the extraction site (Misch and Dietsh, 1993).

Many ARP graft materials have been discussed in the literature, including:

- Autogenous bone (Becker et al., 1994a).
- Autogenous dentine and cementum (Kim et al., 2011a, Park et al., 2015, de Oliveira et al., 2013, Qin et al., 2002, Fugazzotto et al., 1986, Huggins et al., 1970, Nampo et al., 2010), Kim (2012),
- Buccal onlay grafts (Brugnami and Caiazzo, 2011).
- Allograft materials
    - Demineralized freeze-dried bone allograft (Becker et al., 1994a, Becker et al., 1996, Froum et al., 2002a).
    - Mineralized freeze-dried bone allograft (Feuille et al., 2003, Borg and Mealey, 2015).
- Xenograft material (bovine, porcine or equine bone) (Artzi et al., 2000, Mardas et al., 2010).
- Alloplastic polymers (Gross, 1995, Serino et al., 2008).
- Bioactive glasses (Norton and Wilson, 2002, Froum et al., 2002a).
- Composite ceramic materials (Mardas et al., 2010).
- Growth factors and cellular agents (Anitua, 1999, Farina et al., 2013).
- Microbial fibre membranes (Li and Shan, 2011)
- Cell-based bone grafts (Bielby et al., 2007, Livingston et al., 2003, Egusa et al., 2012, Jain et al., 2016, Ciapetti et al., 2006)

The graft material acts to provide a scaffold structure and enhances new bone formation through either osteoinduction (Boyne, 1966), osteoconduction (Albrektsson and Johansson, 2001, Barone et al., 2008) or the intrinsic osteogenicity of the material (Haggerty et al., 2015, Herford and Nguyen, 2015, Araújo and Lindhe, 2011) (*Fig. 4*).

Osteoinduction: The ability of the graft to induce the recruitment and differentiation of mesenchymal stem cells into osteoblasts within the socket area. This mechanism of bone production is often linked to BMP's and also include TGF-β, FGF, ILGF, and PDGF (Boyne and Jones, 2004).

Osteoconduction: The ability of the bone graft material to act as a scaffold for new bone growth, encouraging the migration of external osteoblast cells and vascular elements into the region and allowing new bone formation (Albrektsson and Johansson, 2001, Barone et al., 2008).

Osteogenicity: The potential to form new bone, as a result of osteoid deposition following the activation of osteoblast bone forming cells transplanted from the graft scaffold material (Araújo and Lindhe, 2011, Nevins and Reynolds, 2011).

Whilst the nature of the graft matrix is important, Karageorgiou and Kaplan (2005) proposed that, *in vivo*, the porosity and pore size of the graft material had a significant impact on the level of bone ingrowth into the augmented site, with higher levels of porosity associated with greater levels of bone growth. However, larger particle sized grafts, with greater porosity levels, were considered mechanically weaker, with reduced structural integrity. The choice of particle size utilised in an ARP procedure, should therefore be considered carefully, as it may influence the speed of the bone repair and the rate of remodelling and degradation of the scaffold material (Karageorgiou and Kaplan, 2005). The minimum pore dimension for a graft material was considered to be 100μm, as this ensured adequate space for cell migration. Pore sizes greater than 300 μm were also recommended, as they permitted capillary ingrowth, revascularisation of the site and promoted osteogenesis. The requirement to promote cell migration and bone osteogenesis simultaneously, suggests the need to have a range of particle sizes in an ARP matrix, to ensure optimal tissue regeneration.

As permeability of the graft scaffold is key to bone regeneration, the use of excessive force during placement of the graft should be avoided, to prevent destruction of the porous architecture of the material. Optimal consolidation of the material is however important, as it will reinforce structural tissue support and encourage 3D bone regeneration in the socket (Delgado-Ruiz et al., 2016).

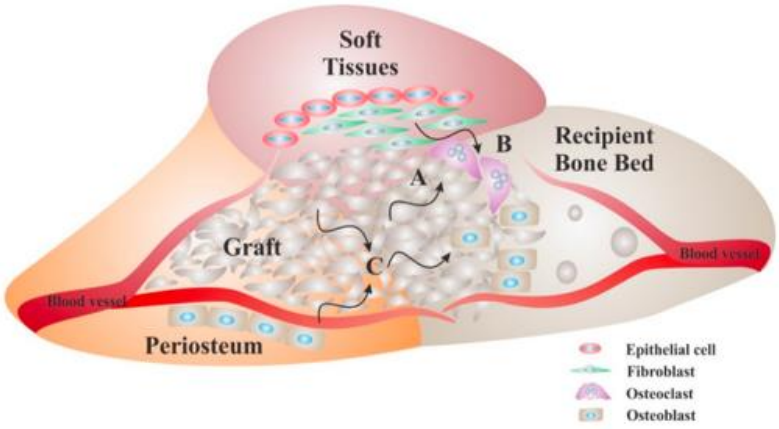


Figure 4. *Bone replacement materials and techniques used for achieving vertical alveolar bone augmentation (Sheikh et al., 2015)*

This review will initially concentrate on the properties of autogenous, allograft, xenograft and alloplast grafting materials and discuss whether immediate implant placement and simultaneous grafting has ability to promote osteogenesis.

Alveolar Ridge Preservation Grafting Materials

1.33 Autogenous bone

An autogenous bone graft is obtained from the same individual undergoing the surgical augmentation procedure. The graft can be harvested intraorally from the tuberosity, mandibular ramus and mandibular symphysis area and extra orally from the iliac crest, rib, tibia, and calvarium (Tomlin et al., 2014). The bone can be cortical or cancellous in nature or can be a mix of both structures. The advantage of using an autogenous graft material is associated with the preservation of the bone, minerals and collagen structure, as well as the transfer of viable osteoblasts and BMPs to the recipient site (Damien and Parsons, 1991). Mesenchymal stem cells within the bone marrow are believed to survive ischemia during grafting, which causes changes in oxygen tension, pH, and cytokine environment. However, several studies have demonstrated that most endogenous cells (probably osteocytes, osteoblasts, and mesenchymal stem cells) on or within autogenous bone undergo apoptosis or necrosis during bone grafting (Atari et al., 2011). Flow cytometry analysis demonstrated that the proportion of viable and apoptotic cells in bone chips collected from maxillary bone was <5% and >95%, respectively (Atari et al., 2011), regardless of the type of instrument, such as piezoelectric devices, scrapers, and rotary mills, used to collect the graft (Yamada and Egusa, 2018).

Whilst the osteoinductive ability due to the presence of growth factors may be variable, autogenous bone also has an osteoconductive ability, due to its scaffold function. In view of these combined osteogenic characteristics, autogenous grafts have been considered the gold standard for regenerative procedures.

Autogenous bone grafts are however associated with several disadvantages, these include morbidity at the harvest site, a limited availability of donor material, patient discomfort and variability in the quality of the harvested bone (Damien and Parsons, 1991). Iliac bone graft material has additionally been associated with root ankylosis and root resorption (Schallhorn, 1972), however these complications have been reduced by freezing the bone in a storage medium or mixing with autologous bone. Harvesting bone from extra-oral sites is a consideration, but this procedure requires the need for additional complex surgery, hospitalisation, increased recovery time and additional site morbidity (De Stavola and Tunkel, 2013).

Autogenous bone can be transplanted as either a cancellous, cortical or a combination bone graft (Diem et al., 1972). Cancellous bone is considered a more superior material, as it contains a higher percentage of cells, rapidly re-vascularises and integrates more readily with the bone in the recipient site. The increase in the cellular components, also means that it has more osteogenic potential and is more likely to stimulate new bone formation. Cancellous grafts have a widespread application in ARP and are generally considered to be easier to manipulate. They can be readily placed or packed into bony socket defects and can be used alone or in combined with other bone substitutes to form composite grafts (Becker et al., 1994a, Becker et al., 1998, Hanser and Khoury, 2014). Cortical bone autografts are considered to be more osseo-substantive

than cancellous grafts, but unfortunately can also be associated with a greater rate of appositional replacement resorption and can occasionally form foci of necrotic tissue (Burchardt, 1983). This necrotic tissue can cause local inflammation and result in greater bone resorption at the placement site.

Although the use of autogenous bone grafts in ARP has been limited, the material has demonstrated an effectiveness in preserving the dimensions of the socket (Hanser and Khoury, 2014, Pelegrine et al., 2010, Donos et al., 2002b). Pinho et al. (2006) described a -1.4mm ± 0.98 reduction in horizontal bone loss when using an autogenous and titanium mesh combination, with Jeng and Chiang (2020), Pelegrine et al. (2010) also confirming a conservancy in height and width measurements with an autogenous graft.

Whilst Chandra et al. (2019) demonstrated a vertical buccal and palatal height gain of 3.09 mm ± 1.22mm and 3.31 ± 2.66 mm, the ability to preserve the contour of the original socket site was variable, as Araújo and Lindhe (2011) observed that autologous grafts have not been found to display any osteoinductive or osteogenetic effects when used for ARP procedures in the dog (Becker et al., 1996). Whilst the graft was readily absorbed and did not interfere with socket healing, it neither stimulated nor retard new bone formation and did not prevent ridge resorption occurring during healing of the extraction socket. Hanser and Khoury (2014) and Pelegrine et al. (2010) found a high level of new bone formation 52% ± 8.6 and 42.87% when using autogenous bone chips and an FGG, at 3m and 6 month healing. The bone core samples had the same percentage as an unassisted healing site, confirming the resorption characteristic outlined by Araújo and Lindhe (2011).

1.34 Allograft bone

Allograft donor material is a non-vital osseous tissue that is derived from human donors. It can be manufactured in either a fresh-frozen, freeze-dried (FDBA), or demineralized freeze-dried (DFDBA) form (Kumar et al., 2013). The use of fresh-frozen allograph was initially associated with problems associated with immunogenicity and viral transmission from the donor. However, this risk has been eliminated with the introduction of FDBA and DFDBA materials, meaning that they are more regularly used in ARP procedures (Froum et al., 2002a, Koutouzis and Lundgren, 2010, Wood and Mealey, 2012, Feuille et al., 2003, Becker et al., 1994a). Both FDBA and DFDBA materials act as an osteoconductive scaffold when they are implanted in mesenchymal tissues. Since FDBA is mineralised and contains calcium and phosphorous salts, it is resorbed more slowly than DFDBA, remaining in the socket for 3 to 12 months after placement (Borg and Mealey, 2015). This slower rate of resorption can result in FDBA becoming surrounded by connective tissue, rather than promoting new bone formation. The advantage of using DFDBA rather that FDBA in an extraction socket was confirmed by Wood and Mealey (2012), who

recorded a significantly greater percentage of vital bone formation (38.42% vs. 24.63%) and a lower mean percentage of residual graft particles (8.88% vs. 25.42%) with DFDBA after 5 months of healing.

The differences in the materials may be associated with the demineralisation process used in the manufacture of DFDBA. Demineralisation of the material leads to the exposure of the underlying bone collagen, facilitating the release of growth factors, including BMP. The release of growth factors increases the osteoinductivity potential of the material, encouraging increased bone formation (AlGhamdi et al., 2010). The extent of the allografts osteoinductivity is dependent on the age of the donor and the amount of bone morphogenetic proteins (BMPs) present in the harvested graft. Grafts obtained from younger donors generally have more BMPs and are considered more osteoinductive.

The osteoinduction ability of allograph materials is still unclear, particularly as Piattelli et al. (1996) demonstrated that only DFDBA particles near the host bone were involved in mineralisation, while in FDBA, even the particles that were farthest from the host bone were lined by osteoblasts and were noted to be actively secreting osteoid matrix. These results point to a more osteoconductive effect from FDBA. This superiority of FDBA was not substantiated in a review of the literature, as Eskow and Mealey (2014) and Iasella et al. (2003) reported a lower level of new bone formation with FDBA.

Due to the differences in the action of the grafting materials, composite grafts are often used to optimize the regeneration of vital bone. FDBA can be combined with DFDBA or autogenous bone, to change the rate of osteoinduction, the substantively of the graft scaffold and the mineral density associated with regeneration (Geurs et al., 2014, Levin, 2013). FDBA and DFDBA has also been incorporated into collagen and polymer matrixes, with growth factors added to further increase the osteogenesis potential (Simon et al., 2009).

Different sizes of allograft have also been examined for their potential for bone development. Hoang and Mealey (2012) examined the effect of using a combination graft particle size in an ARP procedure. No significant difference was found when comparing bone histological healing patterns.

1.34.1 Bone dimensional changes

Grafting of an extraction socket with an allograft matrix, was found to be effective at reducing the amount of vertical and horizontal alveolar bone resorption, when compared to unassisted healing. The dimensional changes reported by ARP studies using allographs, are outlined in Table 9. Investigation of the buccal vertical dimension change following ARP, indicated that a lower level of bone resorption occurred, with less than 1mm of vertical bone loss recorded by most studies (Brownfield and Weltman, 2012, Moghaddas et al., 2012, Toloue et al., 2012, Vance et al., 2004). In some clinical trials no resorption was noted

(Fiorellini et al., 2005), with others demonstrating a bone gain of between 1 and 1.3mm (Hoang and Mealey, 2012, Leblebicioglu et al., 2013) after over-filling of the extraction site. When both the height of the buccal and lingual surfaces were reviewed together (Eskow and Mealey, 2014, Hoang and Mealey, 2012), the level of vertical bone loss was found to be similar, with a loss of between 1mm to 1.94mm reported. The systematic review by Jambhekar et al. (2015) indicated that the loss of buccal wall height was least for DFDBA (0.37 mm), followed by FDBA (0.64 mm), with the lowest reduction recorded with DFDBA+FDBA (0.8 mm). The systematic review by Atieh et al. (2021), indicated a reduction in the loss of mesio-buccal vertical bone height of -3.73 mm (95% CI -4.05 to -3.41) with allograft materials, although the evidence was from only one study

Proximal vertical bone heights suffered less bone loss than mid-crestal positions (Iasella et al., 2003), with no marked differences between the mesial and distal sites reported (Iasella et al., 2003).

The level of horizontal bone resorption was very varied, with allograft and Ca(So4) combination graft only demonstrating a 0.5mm reduction (Vance et al., 2004). A larger horizontal reduction of 2.08mm was recorded by Moghaddas et al. (2012), when reviewing ARP with a DFBA graft. Retention of the horizontal bone appeared to be assisted by combining the allograft material with a barrier membrane (Eskow and Mealey, 2014, Lee et al., 2009, Kim et al., 2011a), with only a small difference in the dimension recorded when using a FBDA or bone ceramic matrix (Mardas et al., 2010).

The systematic review by Jambhekar et al. (2015) indicated that the mean loss of bucco-lingual width at the crest level was 1.63 mm, with the least width ridge dimensions reduction seen with a combination of FDBA and DFDBA (1 mm), followed by FDBA (1.65 mm) and DFDBA (2.18 mm).

Table 9. *Dimensional Changes Following Allograft ARP (mm)*

Author	Time	Intervention	Bone Width	Buccal Bone Height	Lingual Bone Height
(Brownfield and Weltman, 2012)	3m	Allograft Paste	-1.6mm ±0.8 (3mm) 0.8 mm ±0.4 (6mm)	-0.8 mm ±1.2	
(Engler-Hamm et al., 2011)	6m	FDBA copolymer membrane	-3.42 mm or 30%		
(Eskow and Mealey, 2014)	18.2w	Cortical FDBA Cancellous FDBA	-1.5 mm (-0.25 to -2.0.) -2.0 mm (-1.0 to -2.5)	-0.5 mm (0 to -1) -1mm (0 to -1)	-1.1mm ±0.83 -1.94mm ±1.37
(Fiorellini et al., 2005)		BMP-2 + Collagen BMP 2 + Collagen		- 0.6mm ±1.4 0mm ±1.2	
(Hoang and Mealey, 2012)	20w	DBM Allograft		<1mm	<1mm
(Iasella et al., 2003)	5m 7m	FDBA	-1.2mm ±0.9	1.3mm ±2(mid) -0.1mm ±0.7(prox)	
(Leblebicioglu et al., 2013)	?	FDBA and collagen	-2mm to -2.5mm	-0.2mm ±0.3(max) +1.0 mm ±0.3(man)	
(Lee et al., 2009)	5m	Irradiated cancellous allograft Solvent-dehydrated allograft	17.2% 12%	45.9% 46.3%	12% 11.5%
(Mardas et al., 2010)	8m	Bone ceramic	-1.1mm ±1 mm		
(Moghaddas et al., 2012)	4m	DFDBA and connective tissue DFDBA	-1.16mm -2.08mm	-0.72 mm -0.86 mm	
(Nevins and Reynolds, 2011)	5m	Allograft +PTFE) Allograft + buccal overbuild and PTFE Allograft +collagen barrier, and PTFE	-7% -16% -5%		
(Toloue et al., 2012)	3m	FDBA	-1.03 mm ±0.87	0.05mm ±1.46	
(Vance et al., 2004)	4m	Allograft and CaSo4 barrier	-0.50 mm	-0.3mm ±0.7	

Legend: DFDBA, demineralised freeze-dried allograft; FDBA, freeze-dried bone allograft; PTFE, polytetrafluorethylene; Hist, histology; CT, computerised tomography; m, month; man, Mandible; max, maxilla and prox, proximal.

1.34.2 Histological bone formation after allograft ARP

The amount of new bone formation with allograft materials, is reported to be close to that of natural healing, but there exists a significant variation in the range of values recorded (*Table 10*). Eskow and Mealey (2014) reported 12.98% of new bone formation after grafting with cancellous FDBA, in contrast to Hoang and Mealey (2012) who found 52.7% of new bone formation after grafting with DBM allograft.

The addition of PDGF (Wallace et al., 2013, Nevins et al., 2014b), collagen or a Ca(SO4) barrier (Vance et al., 2004) was found to increase the level of new bone formation (Vance et al., 2004, Wang and Tsao, 2008).

This finding was not universal, as Iasella et al. (2003) did not find a difference after using a combination graft, indicating a reduced level of new bone formation (25%) at 7 months. Eskow and Mealey (2014) investigated a combination of FDBA and DFDBA and reported 41.5% of new bone formation and 3.45% of residual graft.

Residual graft matrix was found in most of the ARP studies at 3 months healing, with the least amount (4.5%) recorded after using allograft paste (Brownfield and Weltman, 2012). A high level of residual graft was also found after using a FDBA and collage combination (Iasella et al., 2003). It was unusual that the level of residual graft increased in this study, suggestive that site selection may have played an important part in the variation. Cortical grafts were also observed to have a delayed resorption rate, with a residual graft percentage of 20% at 18-weeks (Eskow and Mealey, 2014).

Beck and Mealey (2010) indicated that the level of fibrous tissue formation was similar in most allograft test groups, within a range 27% to 62%. Variation in the healing time did not appear to be associated with a reduction in the level of fibrous tissue formation.

The systematic review by Jambhekar et al. (2015) found a mean percentage of 29.93% vital bone with alloplastic grafts, 21.75% of residual graft material and 51.03% connective tissue. DFDBA resulted in the formation of 38.42% new bone formation and 8.8% residual graft, while FDBA resulted of 23.54% of new bone and 26.94% of residual graft. A higher level of new bone formation was also observed with FDBA, in the review by Ten Heggeler et al. (2011). However, the systematic review by Chan et al. (2013) found limited evidence to imply that bone formation was higher with either demineralized allografts or autografts. He summarised that both DFDBA and FDBA Alloplastic ARP techniques formed similar levels of new bone, with this new bone percentage less than unassisted healing group.

Table 10. *Histological Characteristics of Sockets Augmented with Allografts*

Author	Time	Material	Bone	Fibrous/connective tissue	Graft Matrix
(Beck and Mealey, 2010)	3m 6m	Human HA Human HA	45.8% ±22.4 45% ±19.8	39.6% ± 13 41.3% ± 14.6	14.6% ±12.9 13.5% ± 12.2
(Brownfield and Weltman, 2012)	3m	Alloplast paste	44.9% Micro CT 37.4% Hist		2.4% Micro CT 4.5% Hist
(Collins et al., 2014)		Human HA	31%		
(Eskow and Mealey, 2014)	18.2w	Cortical FDBA Cancellous FDBA	16.08% (12.12 to 30.25) 12.98% (10.06 to 31.04)	52.9% (47.4 to 57.08) 62.82 (50.89 to 68.51)	28.38% (18.47 to 37.52%) 19.94 (15.82 to 24.33%)
(Fotek et al., 2009)	4m	Human MA and Human Dermal Matrix Human MA and PTFE	27.89% 32.63%	58.19% 52.64%	13.93% 14.73%
(Froum et al., 2002a)	7m	DFBA	34.7%		13.5%
(Hoang and Mealey, 2012)	20w	DBM Allograft	48.8% ±18.7 52.7% ±13.1	43.1 % ±18.6 41.9% ±11.5	8.2% ±4.7 5.4% ±4.5
(Iasella et al., 2003)	5m 7m	FDBA and collagen	31% ±9 25% ±17	37% 34%	32% ±19 41% ±18
(Nevins and Reynolds, 2011)	5m	Mineral collagen bone substitute +PDGF + EMD EMD + bone ceramic	28.3% ±17.2 39.6% ±11.3 23.9% ±9.3 21.4% ±4.2		
(Rodriguez et al., 2014)	4m	Allograft +PTFE) Allograft + buccal overbuild and PTFE Allograft + collagen barrier, and PTFE	28.88% 48.81% 41.13%		
(Toloue et al., 2012)	3m	FDBA	16.7%		21%
(Vance et al., 2004)	4m	Allograft and CaSo4 barrier	61% ±9		
(Wallace et al., 2013)	4m	Allograft Allograft + PDGF	32.5% 41.8%		
(Wang and Tsao, 2008)	5m	Human MA and collagen	68.45%	27.72% ±5.6	3.8% ±3.55
(Wood and Mealey, 2012)	5m	DFDBA FDBA	38.42% ±11.48 24.63% ± 13.65	52.71% ±7.96 49.94% ±11.07	8.8% ± 12.83 25.42% ±17.01

Legend: DFDBA, demineralised freeze-dried allograft; FDBA, freeze dried bone allograft; PTFE, polytetrafluorethylene; PDGP, platelet derived growth factor; Hist, histology; CT, computerised tomography.

1.35 Xenografts

A xenograft bone graft is a deproteinized cancellous bone tissue, which is harvested from a non-human host (Sheikh et al., 2017). Due to the risks associated with immunological reactions, the materials are processed to remove the organic matrix, leaving only the remaining anorganic structure of natural hydroxyapatite, with a 75-80% porosity and a hydroxyapatite structure of between 10nm to 90nm (Barone et al., 2008, Araújo et al., 2015). The graft materials act as an inert osteoconductive filler material, providing a scaffold for new bone formation as well as a source of calcium mineral (Mardas et al., 2010, Riachi et al., 2012).

The xenograft material is a highly biocompatible material, that can be extracted from bovine, porcine or equine animal sources (Festa et al., 2013). It has a carbonate containing apatite structure, with a calcium/phosphate ratio and microstructural composition which is similar to human bone. During healing, the xenograft material becomes integrated into the human bone, with the HA particle potentially resorbed. The remodelling process can take an extended time, with bovine graft material reported in histological samples at 18 months and up to 10-years in sinus graft cases (Artzi and Nemcovsky, 1998, Berglundh and Lindhe, 1997).

Two different preparation processes are predominantly used to prepare xenograft bone tissues. One process uses a low temperature environment (300°C) and chemical NaOH extraction method, to create deproteinised bovine bone mineral (DBBM) such as Bio Oss®. The other technique uses a high temperature environment (≥ 1250 to 1500°C), to remove residual organic structure to create an anorganic bovine bone matrix. The high temperature method results in a larger hydroxyapatite crystal, which has a slower resorption rate. A new innovative process has recently been developed, using a supercritical carbon dioxide ($SCCO_2$). It is proposed that the regenerative property of the porcine grafting material can be improved by the decellularisation process, using $SCCO_2$ extraction technology and CO_2 as a solvent (Huang et al., 2013).

The BioOss® particle (Biomaterials Geistlich, Switzerland) is a DBBM material, that has a porous internal surface and a crystalline structure (Acil et al., 2000), with a 2:1 calcium to phosphorus ion ration. The size of the crystals within the Bio-Oss® material are 10 to 60nm, with the human bone hydroxyl appetite equivalent being 50 to 90nm. The total porosity of Bio-Oss® structure is 60%, which is similarly to human bone (Carmagnola et al., 2003). The porosity of the Bio-Oss® particle surface has been found to promote revascularisation and angiogenesis, creating a scaffold that facilitates bone matrix deposition and osteogenesis (Carmagnola et al., 2003, Berglundh and Lindhe, 1997, Hämmerle et al., 1997).

1.35.1 Dimensional changes associated with xenografts

The successful use of a xenograft material to preserve the alveolar bone dimensions has been demonstrated by researchers (Flügge et al., 2015, Araújo et al., 2015, Barone et al., 2008, Cook and Mealey, 2013, Dies et al., 1996), with the efficacy of embedding the bovine bone mineral, in a 10% highly purified porcine collagen matrix, also validated (Araujo and Lindhe, 2009, Araujo et al., 2008, Sanz et al., 2010, Heberer et al., 2011, Heberer et al., 2008).

The adoption of a xenograft ARP technique was associated with a reduction in the buccal and lingual/palatal vertical bone height and a more variable reduction in horizontal bone dimensional change. A summary of recorded vertical and horizontal bone changes is outline in Table 11. Barone 2008 reported a vertical alveolar ridge reduction of 2.5mm ±1.2 with DBBM, with a small gain of 1.1mm ±0.96 when using a porcine graft matrix. A small loss was however observed by most authors (Mardas et al., 2010, Debel et al., 2021). The range of dimensional bone change, varied from a loss of -1.5mm recorded by Jung et al. (2013b) or an increase of 1.1mm by Barone et al. (2013a). The systematic review by Jambhekar et al. (2015) indicated a mean loss of 0.57 mm buccal wall height, when the measurement was taken from the crest of the ridge, with the systematic review by Atieh et al. (2021) recording a height reduction of (MD -1.35 mm, 95% CI -2.00 to -0.70; $P < 0.0001$) in favour of xenografts.

The degree of vertical bone resorption was found to be less in the interproximal region (Barone et al., 2013b, Mardas et al., 2011), with little variation noted between measurements taken at the mesial or distal proximal positions. The difference between the vertical bone changes in the buccal and lingual aspect of the extraction socket was found to negligible, with the lingual vertical change mostly reported to be less than the buccal change (Fernandes et al., 2011, Jung et al., 2013b) or to have increase in dimension after the grafting procedure (Barone et al., 2008, Barone et al., 2013a, Jung et al., 2013b).

The amount of horizontal bone loss was larger, when compared to the vertical dimensional change and demonstrated greater variation. Fernandes et al. (2011) found a horizontal change of -2.53mm when ARP was undertaken using a DBBM and acellular dermal matrix graft. Gholami et al. (2012) indicated a -1.07mm reduction with a DBBM and collagen technique, with Barone et al. (2012) finding the lowest reduction of -0.75mm, which was associated with a porcine and collagen membrane graft combination. The placement of a porcine graft appeared to reduce the degree of horizontal bone resorption more effectively, with a loss of only -0.75mm (Barone et al., 2012) and -0.15mm (Crespi et al., 2009a) described. The amount of bone resorption was also found to be lower when the width measurements were taken several milometers below the socket margin (Jung et al., 2013b).

Table 11. *Bone Dimensional Change Following ARP with Xenograft Materials*

Author	time	Intervention	Buccal Width	Buccal Bone Height	Lingual and Palatal Bone Height
(Barone et al., 2008)	7m	Bio-Oss®	-2.5 mm ±1.2	-0.7 mm ±1.4	0.4 mm
(Barone et al., 2012)	7m	Porcine bone + collagen membrane	-0.75 mm ±0.3		
(Barone et al., 2013a)	4m	Porcine bone + collagen membrane	-1.6 mm ±0.55	0.3 mm ±0.76 (M) 1.1 mm ±0.96 (Mid) 0.3 mm ±0.85 (D)	0.9 mm ±0.98
(Barone et al., 2013b)	6m	Endobon + collagen Bio-Oss® + collagen	-1.2 mm ±0.8 -1.4 mm ±0.9		
(Brugnami and Caiazzo, 2011)	6w	Buccal onlay + Bio-Oss® graft	-0.85 mm ±0.75		
(Cardaropoli and Cardaropoli, 2008)	4m	DBBM	-1.85 mm (0.5-5.5) 15% of total		
(Crespi et al., 2009a)	3m	Porcine graft	-0.15mm ± 0.1(M) -0.16mm ±0.06 (D)		
(Fernandes et al., 2011)	6m	Bio-Oss® + acellular dermal matrix + p15	-2.53mm ±1.81	-1.2 mm ±2.02	-0.83 mm ±1.53
(Flügge et al., 2015)	3m	Bio-Oss®	-0.8mm		
(Gholami et al., 2012)	6-8m	DBBM + collagen	-1.07mm		
(Jung et al., 2013b)	6m	Bio-Oss® collagen + collagen membrane Bio-Oss® collagen + connective tissue graft	-1.2 mm ±0.8 -0.6 mm ±0.6 -0.1 mm ± 0.2± 1.4 mm ±1.0 0.6 mm ±0.5 0.6 mm ±0.9	-1.5mm ±1.2 -0.5 mm ±1	-0.4 mm ±1.4 +0.3 mm ±1.1
(Kim et al., 2011b)	3m	DBBM + collagen	-20.74%		
(Kotsakis et al., 2014b)	5-6m	Bio-Oss®	-1.39 mm ±0.57		
(Mardas et al., 2010)	8m	Bio-Oss® + collagen	-2.1 (±1.0)		
(Mardas et al., 2011)	8m	Bio-Oss® + collagen		-0.4 mm ±1.3 -0.7 mm ±1.3	
(Neiva et al., 2008)	4m	Bovine bone + P15 + collagen	-1.31 mm ±0.9	-0.15mm ±1.76	
(Pang et al., 2017)	6m	Bio-Oss®	+6.5 mm ± 3.54 From base of socket		
(Patel et al., 2013)	12m	Bio-Oss® + collagen	-2.1 mm ±1.0	0.2 mm ±0.7	
(Vance et al., 2004)	4m	DBBM + collagen		0.7 mm ±1.2	
(Debel et al., 2021)	6m	DBBM + FGG DBBM +Gelatin sponge	-7.1 mm -4.0 mm -2.5 mm 4.8 mm 2.3 mm 1.3 mm	-0.8 mm ± 0.6 -0.7 mm ± 0.5	

Legend: DBBM, deproteinised bovine bone matrix; FGG, free gingival graft; P15, P15 peptide M, mesial; Mid, middle and D, distal.

Marked variation in degree of horizontal tissue loss (-0.4mm to -1.5mm) was observed when examining the results of ARP with a Bio-Oss® grafting material (Mardas et al., 2011, Jung et al., 2013b, Barone et al., 2013c, Gholami et al., 2012).

The systematic review by Jambhekar et al. (2015) compared ARP xenograft techniques against extraction alone, describing a mean loss of bucco-lingual width at the crest level of 1.3mm. A similarly designed systematic review by Atieh et al. (2021), indicated that there was a very low certainty of evidence, that the technique was associated with a reduction in the alveolar ridge width (MD -1.18 mm, 95% CI -1.82 to -0.54; P = 0.0003). The conclusion from this systematic review was that there was no evidence to indicate the superiority of a specific xenograft grafting materials, when height and width measurement were reviewed follow ARP procedures.

1.35.2 Histological changes associated with xenograft materials

The ability of a bovine, equine or porcine xenograft matrix to promote new bone formation, has been demonstrate in several studies (*Table 12*)**.** The percentage of new bone formation has however been found to be variable, ranging from 9% (Park et al., 2010) to 47 % (Cook and Mealey, 2013). Equine bone appears to create a lower level of new bone formation, when compared to bovine sources (Park et al., 2010).

Calasans-Maia et al. (2014) examined the effect of using two different xenograft materials, after 6 months healing. The bone core samples indicated a mean new bone formation of 33.7% (± 7.1) and 32.3% (± 8.9), with a residual graft percentage of 10.7% (± 16.2) and 19.3% (± 22.6). Xenograft bone healing was examined in the systematic review by Jambhekar et al. (2015), who indicated a mean new bone formation percentage of 35.72%, a residual graft percentage of 19.30%, with 44.42%, connective tissue. The systematic review by Chan et al. (2013) also recorded a comparable result, with the mean percentage of vital bone ranging from -22.2% (decrease) to 9.8% (increase), when compared to unassisted healing.

The resorption characteristics of a xenograft matrix were found to be different to that of the allograft matrix, as an increase amount of residual material remained after a 9 month healing period (Ayna et al., 2015, Testori et al., 2013, Riachi et al., 2012). The increase in residual graft material was associated with a lower level of new bone formation (Heberer et al., 2011, Park et al., 2010, Nam et al., 2011) and less connective tissue matrix (Vance et al., 2004, Norton et al., 2003, Lee et al., 2009). Chan et al. (2013) concluded that the connective tissue content decreased as a direct consequence of the additional residual xenograft matrix (15% to 36%), the graft remaining unresorbed at 5.6 months healing.

Although some studies have suggested that the variation in the maturation rate was independent of the presence of the grafting material (Heberer et al., 2008), with the variation caused by differences in the sample site, the potential for the xenograft matrix to delay the bone healing response was regularly reported (Heberer et al., 2011, Araújo et al., 2009, Lindhe et al., 2014).

As osteoclastic multi-nucleated cells have been observed on the surface of the xenograft particles, with scalloping seen on the edge of the particles (Hämmerle et al., 1998, Hämmerle et al., 1997, Tapety et al., 2004), it has been suggested that continued resorption of the xenograft particle does occur, but over an extended period. The slower resorption process eventually resulting in the replacement of the graft scaffold. A more detailed description of graft matrix resorption characteristics is discussed in Chapter 1, Section 38.

***Table 12**. Histological Healing Characteristics Following ARP With Xenograft Materials (%)*

Author	time	Material	Bone	Fibrous/connective tissue	Graft Matrix
(Artzi et al., 2000)	3m	DBBM	46.3% ± 9.81	51.6% ± 36.1	
(Barone et al., 2008)	7m	Cortico-cancellous porcine bone	35.5% ± 10.4	36.6% ± 12.6	29.2% ± 10.1
(Barone et al., 2013b)	6m	DBBM + collagen	28.5% ± 20 31.4% ± 18		
(Cardaropoli and Cardaropoli, 2008)		DBBM + collagen			24.5% ± 11.65
(Cardaropoli et al., 2012)	4m	DBBM + collagen	26.34% ± 16.91	55.19% ± 11.45	18.46% ± 11.18
(Cook and Mealey, 2013)	5m	Bio-Oss® Collagen Xenograft sponge + bovine collagen	32.83% ± 14.72 47.03% ± 9.09	53.73% ± 6.76 52.9% ± 9.09	13.44% ± 11.57 0.0%
(Crespi et al., 2011a)	4m	Porcine Graft	38.0% ± 16.2	36.6% ± 4.8	25.3% ± 9.4
(Froum et al., 2004)	7m	Bio-Oss® with acellular dermal matrix Bio-Oss® + e-PTFE	41.7% 17.8%		
(Gholami et al., 2012)	6-8m	DBBM + collagen	28.63% ± 12.55		
(Heberer et al., 2011)	3m	Bio-Oss®	24.4% ± 10.8	14.75% ±6.98	60.85% ± 8.78
(Lee et al., 2009)	5m	DBBM	23.6%	34.1%	25.4%
(Lindhe et al., 2013)	+6m	Bio-Oss® /Mucograft®	39.9% ± 8.6	32.4% ± 9.2	19.65% ± 6.5
(McAllister et al., 2010)	3m	PDGF + Bio-Oss®	24%		
(Nam et al., 2011)	6m	DBBM + Oligopeptide + Collagen DBBM + Collagen	10.4% ± 4.6 5.3% ± 8.3	70.8% ± *8.7* *78.3% ± 19.5*	18.7% ± 7 16.4% ± 12.2
(Neiva et al., 2008)	4m	Bovine bone + P15 + collagen			6.25%
(Norton et al., 2003)	4m	Bio-Oss®	26.9% (4m) 28.9% (6-10m)	47.4%	25.6%
(Pang et al., 2017)	6m	Bio-Oss®	35% ± 19.33		
(Park, 2010)	6m	DBBM + acellular dermal matrix	39.4%		
(Park et al., 2010)	4	Equine BM	9.88% ± 6.57	47.5% ± 9.28	42.62% ± 6.57
(Perelman-Karmon et al., 2012)	9m	DBBM	29.7% ± 7.21		
(Perelman-Karmon et al., 2012)	9m	DBBM + collagen	40.8±% ± 10.61		
(Vance et al., 2004)	4m	DBBM + collagen	26% ± 20	59%	16% ± 7
(Villanueva-Alcojol et al., 2013)	9m	Porous bovine bone	23.3%	49.2%	27.5%
(Lai et al., 2020)	20W	DBBM +PTFE	36.21%	43.32	20.47

Legend: DBBM, deproteinised bovine bone matrix; FGG, free gingival graft; PTFE, polytetrafluoroethylene; P15, P15 peptide.

1.36 Alloplast bone grafts

Calcium sulphate (CaSo4) is an alloplast synthetic bone substitute that acts as a biologic filler within the extraction socket. It has osteoconductive bone properties and does not require a donor site for preparation. It is manufactured to resemble natural bone and is non-allogenic in nature (Kutkut et al., 2012). The original calcium sulphate was Plaster of Paris, which was found to be non-inflammatory, nonreactive, and was observed to encouraged bone healing in a contained lesion (Kim et al., 1999). The material was observed to form a bond to the socket bone, promoting new bone development through the deposition of natural appetite on the alveolar surface and cellular interaction with osteogenic cells. The material has limited osteoconductive capability, so can become surrounded by a dense fibrous tissue matrix, if it is not placed in close proximity to bone (Giannoudis et al., 2005).

Tri-calcium phosphate (TCP) or Ca3(PO4)2, is a porous, osteoconductive grafting material, with a small size and a porosity diameter of 100–300μm. It is rapidly broken down and resorbed by the body, creating a calcium and magnesium ions concentration in the local tissue. This ionic environment simulates healing, inducing an alkaline phosphatase activation, which is fundamental for bone synthesis (Rodella et al., 2011)

Polymethylmethacrylate has been used as a degradable and nondegradable polymer bone grafting material for over 40 years. It is cheap to produce and can be readily contoured to fit the surgical extraction socket. It has limited osteogenic and no osteoconductive capacity, with a macrophage reaction seen to result in increased bone resorption. Their use in ARP procedures has been limited to long-term site preservation, without implant placement.

Bioactive glasses are an osteoconductive bone substitute, composed of sodium oxide, calcium oxide, phosphorus pentoxide, silicon dioxide, and silica. They promote bone development by the formation of a biologically active hydrated calcium phosphate layer at the surface of the glass, with this layer undergoing mineralisation with hydroxyapatite crystals, when in close proximity to bone (Dimova, 2014). Small particle bioactive glass is considered osteoconductive and resorbable, but fibrous encapsulation can occur if large particles are placed away from the bone surface (Yilmaz et al., 1998).

PMMA acts as a bone scaffold for new bone formation, with **Coralline hydroxyapatite** (HA) graft material viable as a long-term ARP agent. The material resembles cancellous bone, having a dense HA structure which acts as an osteoconductive scaffold, to promote bone ingrowth into the porous particle (Bartee, 2001, Trombelli et al., 2002).

Biodegradable polymers are regarded as a more versatile material, as they can be used alone or in combination with other materials (Gross, 1995, Serino et al., 2008). Polylactic acid and Polyglycolides are synthetic biodegradable polymers, which are being manufactured as sponges to a delivery agent for growth

factors. They have some disadvantages, as they have a variable resorption rate, do not always act as a substantive scaffold to promote bone regeneration and are poorly hydrophilic (Wang et al., 2005).

1.36.1 Alloplast bone dimensional changes

A reduction in the amount of vertical and horizontal bone alveolar bone resorption, has been documented when using ARP with an alloplast material (Aimetti et al., 2009, Clozza et al., 2012, Gholami et al., 2012, Kotsakis et al., 2014a), with experiment findings outlined in Table 13.

These studies have indicated that use of CaSo4 and TCP materials, has been associated with a mid-buccal vertical dimensional loss between -0.5mm and -1.33mm (Aimetti et al., 2009, Toloue et al., 2012), with bio-ceramics sometimes displaying a slight increase in height of -0.7 (±1.1mm) when compared to unassisted healing (Mardas et al., 2011, Patel et al., 2013). An increase in the magnitude of the vertical bone loss was observed on the buccal aspect of the socket, when compared to the lingual surface (Jung et al., 2013b, Clozza et al., 2012). A reduced level of vertical change was nevertheless observed in the proximal sites, when compared to the mid-buccal position (Crespi et al., 2009a, Serino et al., 2003). An extended healing time did not appear to affect the level of vertical bone loss when bone ceramics or synthetic HA were used (Crespi et al., 2009a, Patel et al., 2013, Yilmaz et al., 1998).

The use of a multiple component graft material did not appear to produce a discernible difference in the level of the vertical height reduction when compared to unassisted healing (Vance et al., 2004, Mardas et al., 2011, Huh et al., 2011). The systematic review by Jambhekar et al. (2015) reported a mean loss of buccal wall height of 0.77 mm, when using alloplast material.

The level of horizontal dimensional changes was reduced when using both CaSo4, TCP and Bio-glass graft matrices, with an overall reduction of 0.6mm to 2mm of horizontal bone loss recorded (Aimetti et al., 2009, Clozza et al., 2012, Yilmaz et al., 1998, Jung et al., 2013b). A longer healing period resulted in progressive bone change and further tissue reduction, when sites were grafted with a Bio-glass matrix (Yilmaz et al., 1998). Bone ceramics have been found to increase the width of the alveolar ridge (Patel et al., 2013), but the systematic review by Jambhekar et al. (2015) reported a mean loss of the buccolingual width of 2.13 mm with alloplast material.

Table 13. *Dimensional Change Following ARP with Alloplast Materials*

Author	time	Intervention	Bone width	Buccal vertical bone height	Lingual/ palatal vertical bone height
(Aimetti et al., 2009)	3m	CaSo4	-2.0 mm ± 0.6	-0.5 mm ±1.1(Mid) -0.2 mm ±0.6 (Prox)	
(Clozza et al., 2012)	3m	Bio-glass	-1.8 mm ± 1.1 (77%)	2.7 mm ±1.1	1.9 mm ±1.2
(Crespi et al., 2009a)	24m	Magnesium HA CaSo4		-0.21 mm ±0.08 (M) -0.22 mm ±0.09(D) -0.14 mm ±0.07(M) -0.12 mm ±0.11(D)	
(Crespi et al., 2009b)	3m	Magnesium HA CaSo4		-0.48mm ±0.21 -2.48mm ±0.65	
(Gholami et al., 2012)	6-8m	Nano crystalline bone	7.36 mm ±1.94 to 6.43 mm ±2.08		
(Huh et al., 2011)	3m	BMP-2 with beta-TCP/ beta-TCP/HA	25% -1.28 mm ±1.39 50% -0.54 mm ±1.16 25% -0.01 mm ±1.15 50% -1.24 mm ±1.25	-0.059mm ±0.960 -1.09 mm ±1.413	
(Jung et al., 2013b)	6m	TCP + poly lactic acid	6.1 mm ±2.5 3.1 mm ±1.6 5.7 mm ±3.0	-3.9 mm ±2.4	-0.4mm ± 1.4
(Kotsakis et al., 2014b)	5-6m	CaPo4	-1.26 mm ±0.41		
(Mardas et al., 2011)	8m	Bone ceramic + collagen membrane		-0.9 mm ±1.2 (M) -0.7 mm ±1.8(D)	
(Patel et al., 2013)	12m	Bone ceramic + Collagen	0.4 mm ±1	1.1 mm ±1	
(Serino et al., 2003)	6m	Bioabsorbable synthetic sponge of polylactide-polyglycolide		-0.2 mm ±1.4 (M) +1.3 mm ±1.9 (Mid) -0.1 mm ±1 (D)	
(Toloue et al., 2012)	3m	Ca So4	-1.33mm ±1.22	-0.23 mm ±1.69	
(Vance et al., 2004)	4m	Allograft + putty carrier + CaSo4		-0.3 mm ±0.7	
(Yilmaz et al., 1998)	12m	Bio-glass cones	-0.6 mm ±/0.66(3M) -0.8 mm ±0.66(12M)	-0.2 mm ±0.58 (3M) -0.2 mm ±0.34 (12M)	
Legend: TCP, tri-calcium phosphate; HA, hydroxy-appetite and BMP, bone morphogenic protein; M, mesial, Mid, Middle; D, distal; Prox, proximal.					

1.36.2 Histological changes associated with alloplastic materials

The capacity of an alloplast matrix to promote new bone formation following ARP, has been suggested (*Table 14*). Although the percentage of new bone formation was found to vary from 21% (McAllister et al., 2010) to 66.7% (Serino et al., 2003), the level of new bone formation was found to be similar to that of unassisted socket healing (Aimetti et al., 2009, Clozza et al., 2014, Froum et al., 2002a).

The amount of residual graft remaining in the samples was low when using TCP and CaSo4 allografts (Aimetti et al., 2009, Brkovic et al., 2012, Crespi et al., 2009b, Mahesh et al., 2012, Ruga et al., 2011, Guarnieri et al., 2004), with higher levels recorded with synthetic HA and magnesium derivatives (Checchi et al., 2011, Crespi et al., 2009b, Kim et al., 2013). These low levels suggest rapid resorption of the graft matrix and early replacement by new bone. Bio-glass and coral graft matrices (Clozza et al., 2014, Molly et al., 2008) were also noted to promote comparable bone healing, with polylactic and polyglycoside use resulting in the production of high levels of new bone formation and no residual matrix.

Combining the allograft matrix with collagen materials (Brkovic et al., 2012, Nevins et al., 2012, Nevins et al., 2011, Kim et al., 2013), or other alloplast materials (Kim et al., 2013) (McAllister et al., 2010) did not appear to increase the amount of new bone formation. Some combination ARP allograft studies demonstrated a reduction in new bone formation (McAllister et al., 2010, Brkovic et al., 2012) when compared to the using a singular graft matrix, suggestive that normal healing had been delayed following ARP. Increasing the healing period, did not produce a marked increase in new bone formation (Brkovic et al., 2012, Kim et al., 2013, Froum et al., 2002a), with similar levels of fibrous tissue formed in most sites. The fibrous and connective tissue percentage conformed to averages found for normal socket healing. The systematic review by Chan et al. (2013) indicated an overall increase in new bone formation of between 6.2% to 23.5% when use of an alloplast was compared to nongrafted sites.

Table 14. *Histological Healing Characteristics Following ARP with Alloplast Materials*

Author	Time	Material	Bone	Fibrous/connective tissue	Graft Matrix
(Aimetti et al., 2009)	3m	CaSo4	58.8% ±3.5		
(Brkovic et al., 2012)	9m	TCP + collagen TCP + collagen cone + membrane	42.4%±14.6 45.3% ±14.5	47.1% 42.1%	9.7% ±7.3 (Serino et al., 2008) 12.5% ±6.6
(Checchi et al., 2011)	6	Biomimetic HA Nano-crystalline HA	54% ±22 49% ±28	39% 41%	8% ±7 14% ±7
(Clozza et al., 2014)	6m	Bio-glass	54% ±31		8.1% ±7.8
(Collins et al., 2014)	7-12m	CaSo4	33%		
(Crespi et al., 2009b)	4-6m	Magnesium HA + collagen CaSo4 + collagen	40% ±2.7 45% ±6.5	41.3% ±1.3 41.5% ±6.7	20.2% ±3.2 13.9% ±3.4
(Crespi et al., 2011a)	4m	Synthetic Magnesium HA + Alloplast	36.5% ±2.6	32.2% ±3.2	33.3% ±1.5
(Froum et al., 2002a)	6-8m	Bioactive glass	59.5%		5.5%
(Gholami et al., 2012)	6-8m	Nano crystaline bone	28.63% ±12.53		
(Guarnieri et al., 2004)	3m	CaSo4	58.1% ±6.2		

Legend: TCP, tri-calcium phosphate and HA, hydroxy-appetite.

1.37 Summary of socket healing following bone grafting

There is strong evidence from clinical trials that ARP procedures using a grafting material, are more effective at preserving the dimensions of the extraction socket than unassisted healing (Barone et al., 2008, Cardaropoli and Cardaropoli, 2008). The benefits of using a bone matrix graft have been contested by some researchers (Nevins et al., 2006, De Coster et al., 2011, Serino et al., 2008), as the presence of a graft material has sometimes been identified as interfering with the normal tissue healing process (Becker et al., 1998, Buser et al., 1998, Lindhe et al., 2014). Particularly as marked differences have been observed in the quantity and the quality of the regenerated bone tissue (Froum et al., 2002; Mardas et al., 2010; Horvath et al., 2013; Hsun-Liang et al., 2013). The differences in healing are characterised by an increase in the connective tissue composition, which is suggestive of delayed healing (Lindhe et al., 2014, Dies et al., 1996, Araujo et al., 2008).

Histological studies have indicated that residual graft particles can be found surrounded by a combination of connective tissue and new bone at 6 to 9 months after insertion (Nevins et al., 2006, Becker et al., 1998, Becker et al., 1994a, Artzi et al., 2000, Carmagnola et al., 2003), indicative of incomplete bone healing at the ARP site. This alteration in the healing process may be related to the resorption characteristics of the material, as the presence of the bone scaffold may invoke a giant cell, foreign body response, with delayed activation of the osteoclastic process (Serino et al., 2008). Norton and Wilson (2002) indicated that new bone formation could only be seen histologically after 6 months of healing with bioactive glasses, with Zitzmann et al. (2010) and Wood and Mealey (2012) reporting poor resorption rates of synthetic FDBA after 5 months of healing.

Evidence of a delayed healing response was observed by Heberer et al. (2008), when examining ARP with a xenograft material. Although the xenograft appeared to be eventually incorporated into the natural bone, its low resorption rate could negatively impact on the healing of the grafted site (Camelo et al., 1998) and compromise the mechanical and biological properties of the regenerated tissue. Tatum Jr (1995), Artzi et al. (2000) and Carmagnola et al. (2003) suggested that grafting of intra-oral and implant sites with xenografts, resulted in the retention of between 30 – 40% of the graft matrix at 9 month, with the retained particles surrounded by vital, newly formed bone. In implant sites, the newly formed bone was observed to separate the remaining xenograft particles from the implant surface (Rodella et al., 2011), with the residual graft not observed to influence the osseointegration of the implant fixtures.

When a porcine xenograft substitute was used as an alternative scaffold (Thalmair et al., 2013), histological analysis indicated an almost complete incorporation of the cortico-cancellous particles, which were surrounded by vital bone. This characteristic was in agreement with the histological results reported by Barone et al. (2008). In contrast to the previous studies , other investigators found that the use of a bovine

bone substitute resulted in incorporation of the graft particles in connective tissue , with only a small amount of newly formed bone (Carmagnola et al., 2003, Araujo and Lindhe, 2009, Araújo et al., 2010).

A systematic review of the histological composition of the healed socket, following AR, was undertaken by Chan et al. (2013). He concluded that based on the limited number of prospective comparative studies, the use of grafting materials for socket augmentation might change the proportion of vital bone formation. Whether these changes in bone quality will influence implant success and peri-implant tissue stability remained unknown. Cardaropoli et al. (2003) suggested that less than 40% of graft particle should be retained within the healed extraction socket if successful implant placement was to be achieved. The importance of this percentage, has not been substantiated by another researcher

The suitability of an intact extraction socket, as a test for the osteogenic potential of a graft material has also been questioned (Mellonig and Towle, 1995). The authors proposed that only two responses could occur following socket grafting, either the graft material has no influence on natural healing, or the graft material would impair the healing process. Consequently, test and control sites would yield, at best, the same healing bone characteristic, with the grafted site potentially having a slower healing rate than the control. Enhanced bone formation would only occur if a GBR procedure was undertaken. This view would necessitate that a delayed protocol for reconstruction of the extraction site is required, or that primary soft tissue closure and the adoption of a GBR procedure is necessary to facilitate additional new bone formation. Although subsequent studies have failed to corroborate the statistical inferiority of grafting alone in ARP procedures (Kim et al., 2013, Kim et al., 2012), a delay in the healing time is often reported both with grafting alone and in conjunction with GBR.

The interpretation of graft and bone integration levels is also a concern, as radiographic density measurement, may be erroneously extrapolated to represent histological healing in animals and human studies. This lack of clarity may lead to the mistaken conclusion, that the graft material has been successfully “osseointegrated” into the extraction socket site (Norton and Wilson, 2002).

In summary, it can be concluded that graft scaffolds can be successfully used for ARP procedures, despite their slow resorption rate, and the potential for retention of graft particles within the socket site over an extended period (Kotsakis et al., 2014a). The time frame for new bone development may however be delayed, necessitating the need for a prolonged healing period, a type IV delayed implant placement protocol (Kim et al., 2012), or guided bone regeneration prior to the consideration of implant placement (Heberer et al., 2011). Attempting surgery without compensating for the delayed healing of a grafted socket may lead to an inability to successfully place the implant and result in inadequate primary stability. The influence of the retention of graft particles in the success and outcome of implant treatment is inconclusive.

1.38 Other ARP Techniques

1.38.1 Collagen matrix

A collagen matrix can be readily placed in the extraction socket and provides excellent haemostasis by physical compression of the wound. It accelerates tissue regeneration and enhances natural healing by protecting the extraction site from the inflow of food and debris, whilst preventing soft tissue collapse during the initial healing phase (Bartee, 2001). The material has excellent biocompatibility and low antigenicity and readily biodegrades, helping to promote new bone conductivity (Lee et al., 2001).

1.38.2 Microbial fiber membrane

Microbial fiber membranes have been investigated as an ARP agent, due to its promotion of wound healing and its anti-inflammatory ability after tooth extraction (Li and Shan, 2011). In the animal model, the results of the histologic examination indicated MF-FLA could facilitate the growth of fibroblasts and osteoblasts and inhibit inflammatory cells. In human trials, the results indicate that MF-FLA can promote early wound healing and reduce the incidence of post extraction complications because of its biocompatibility, anti-inflammatory ability, and support to the formation of a blood clot in the tooth socket (Li and Shan, 2011). This stabilisation effect, resulted in superior radiographic bone wound healing, when compared to unassisted healing.

1.38.3 Cell-based bone grafts

The development of stem cell isolation and culture has led to further opportunities for bone development (Bielby et al., 2007). Mesenchymal stem cells (MSC) can be obtained from human bone marrow in the jaw and skeletal tissue, umbilical cord and adipose tissue and used in combination with a carrier agent to promote bone development (Livingston et al., 2003, Egusa et al., 2012). These cells have the capability to differentiate into osteoblasts or bone forming cells, inducing increases angiogenesis and osteogenesis within the extraction site (Jain et al., 2016), through the release of cytokines and growth factors (TGF) to encourage angiogenesis and wound healing. The effectiveness of the MSC as an ARP agent was recorded as being enhanced by the presence of a carrier with osteoconductive potential, as the combination graft material allowed the formation of an inductive microenvironment to support natural bone regeneration (Jain et al., 2016, Ciapetti et al., 2006).

Jain et al. (2016) examined the difference between a test ARP group using MSC and an unassisted healing control. The study found a difference in the mean width measurement of -1.42 mm at 2 below the CEJ, -

1.2mm at 5mm and -1.02 mm at 8mm. The difference in mean values between control group and test group was found to be statistically significant in bucco-lingual (BL) and mesio-distal dimension at 5 mm and in the BL dimension at 8 mm, with more bone formation in the test group compared to the control at 3 and 6-months

1.38.4 Dentine and cementum grafts

Alveolar bone and tooth structures are formed from similar embryological origins, with many common proteins and growth factors present in both tissues (Qin et al., 2002). These biological similarities have led researchers to investigate the use of dentine and cementum tissue as a viable replacement for autogenous bone graft material in the oral environment (Fugazzotto et al., 1986, Huggins et al., 1970).

Animal investigations demonstrated that sterile particulate dentin could be successfully used as an alveolar bone augmentation material (Huggins et al., 1970, Fugazzotto et al., 1986, Nampo et al., 2010), with the augmented area characterised by the integration of the graft material and the creation of new bone.

This initial success led to the development of a human demineralized dentine matrix (DHDM) and its application in ARP procedures. de Oliveira et al. (2013) found that DHDM and cementum could act as a scaffold for osteoblast differentiation, yielding superior new bone formation, when compared to unassisted healing. Kim (2012) confirmed that DHDM ARP sites developed a viable bone composition, which was compatible with future implant placement. The new bone was formed through space maintenance and the release of BMPs, which promoted cellular differentiation, osteoblast migration and increased osteogenesis (Kim et al., 2010). The histological differences between an autogenous dentine and bovine bone graft was reviewed by Pang et al. (2017). No statistical difference was found between the two groups, with histological examination indicated the absence of infection at both graft sites, with the creation of 31.24% (± 13.87) of new bone formation with the dentine matrix and 35.00% (± 19.33%) with the xenograft material. After 6-months, the vertical dimension of the alveolar bone was increased by 5.38mm (± 2.65) when using the dentine matrix and 6.56mm (± 3.54) mm in the xenograft groups period.

The use of dentine as an alternative graft material was not universally accepted, as Kadkhodazadeh et al. (2015) found that dentine and cementum particulate grafts offered no improvement in bone regeneration in alveolar extraction sockets compared to controls.

1.38.5 Root submergence and socket-shield technique

The simplest and the most advantageous method to preserve the alveolar tissue is to prevent the loss of the root, inhibiting the physiological and dimensional changes experienced during healing of the extraction

socket. This submucosal "root retention effect" was initially promoted as a method to maximize the stability of a removable prostheses (Osburn, 1974, Firtell et al., 1979) or to facilitate pontic site development (Salama et al., 2007), as it acted to potentiate the regeneration of an epithelial layer, whilst maintaining the integrity of the bundle bone and periodontal ligament and reducing the disruption to the local blood supply. The adoption of the technique was however limited, because fracture of the tooth, or the presence of root caries or endodontic pathology (Avila-Ortiz et al., 2014a) often necessitated removal of the root.

The advantages of retaining a component of the root structure has now been investigated as a method to facilitate implant placement with (Malmgren, 2013, Avila-Ortiz et al., 2014a, Garver and Fenster, 1980). Sperling et al. (1986), and Malmgren (2013) indicated that de-coronation and preservation of an ankylosed root, acted to maintain the buccal/palatal alveolar dimension, with Park et al. (2007) suggesting that the technique led to an increase in the vertical height of the ridge. Davarpanah and Szmukler-Moncler (2009) and Scheuber et al. (2013) reported on several cases where the implant osteotomy site had been undertaken through a retained ankylosed roots, where the root fragments were deliberately left in place. The histological results indicated that successful osseointegration of the fixture occurred, with the retained root fragments either remaining asymptomatic or the dentine slowly resorbed over time and substituted by bone (Malmgren et al., 2006).

The principles of the root retention technique have now been adapted (Hurzeler et al., 2010, Baumer et al., 2015, Kan and Rungcharassaeng, 2013, Siormpas et al., 2014, Cherel and Etienne, 2014b, Glocker et al., 2014), with (Hürzeler et al., 2010) proposing "***the socket shield technique***", in which a partial root fragment is retained in front of, or in contact with, an immediately placed implant to preserve the buccal bone. Although the technique has demonstrated successful buccal tissue preservation and clinical success in the short term (5-years), histological examination found a cementum and periodontal attachment to the implant surface, which may be indicative of a fibrous union (Baumer et al., 2015) and incomplete osseointegration in the area (Parlar et al., 2005) which may pause a risk for the development of peri-implant infection in the area.

To prevent these adverse events occurring, (Glocker et al., 2014) supported a modification to the technique, where a buccal root fragment, just large enough to meet the minimum requirements, was preserved, with the implant placement delayed to 6-months after the extraction. The technique was not advocated in the lingual area, as the bundle bone is normally thicker and less prone to atrophy in this region, with an increased risk of damage to blood vessels and nerves structures if pursued (Glocker et al., 2014).

In another study (Kan and Rungcharassaeng, 2013), a further modification to the approach was reported, where a proximal root fragment was maintained in the mesial and distal papilla area, to preserve the tissue contour. This proximal shield technique was trailed by (Cherel and Etienne, 2014a), who indicate that the

technique was successful in preserving the papillary height, and facilitating successful integration of the implant over the short term.

1.38.6 Buccal onlay grafts

A novel approach to preserving the buccal bone dimension has been proposed by (Brugnami and Caiazzo, 2011), who suggested that a xenograft matrix should be placed on the external buccal aspect of the socket rather that within the extraction socket defect. The rationale for this procedure being that the slow or non-resorbing particles of the xenograft might be incorporated between the soft and hard tissues and prevent resorption of the newly regenerated bone in the adjacent tissue. This technique has been reported as reducing dimensional change, with an animal study by Birang et al. (2019) demonstrating its effectiveness at preserving alveolar dimensions.

Alveolar Ridge Preservation using Guided Bone Regeneration and Socket Seal Techniques

1.39 GBR techniques

The principles of GBR are based on the guided tissue regeneration (GTR) principles established in the late 1980s (Dahlin, et al. 1988). The procedure requires the surgical placement of an occlusive barrier membrane, to physically isolate the bone site where regeneration is being attempted (Elgali et al., 2017). It aims to create a segregated space, which facilitates the recruitment, proliferation, and migration of pluripotential and osteoprogenitor cells from the marrow spaces and or the endothelium of the new vasculature, directly into the regeneration area (Dahlin, et al., 1980, Schenk, et al. 1994). The occluding barrier mechanically prevents the in-growth of non-osteogenic epithelial and fibroblast cells from the overlying mucosa, facilitating repopulation of the osseous wound with osteogenic cells originating from the defect (Retzepi and Donos, 2010, Dahlin et al., 1990). The GBR technique is considered a successful method to promote ARP (Mezzomo et al., 2011) and socket healing (Horváth et al., 2013, Jung et al., 2004).

GBR ARP procedure can be used with a barrier membrane alone (Lekovic et al., 1998, Pagni et al., 2012, Avila-Ortiz et al., 2014b, Dies et al., 1996, Rodriguez et al., 2014, Vance et al., 2004) or in combination with particulate bone grafts or bone substitute (Adriaens and Van der Stede, 1998, Iasella et al., 2003, Mardas et al., 2011, Mardas et al., 2010).

Primary closure of the gingival tissues is often advocated as a component of the procedure, to allow complete coverage of the membrane overlying the extraction socket (Wessing et al., 2018). The tissue advancement protecting the extraction site from bacterial contamination and preventing loss of the graft substitute (Pagni et al., 2012).

1.39.1 ARP GBR membranes

The literature describes a number of barrier membranes that can be utilised at the time of tooth extraction (Liu and Kerns, 2014).

The membranes are normally separated into resorbable or non-resorbable materials. They include:

a. Non-Resorbable Membranes:

- Expanded polytetrafluoroethylene (e-PTFE)
- High-Density Polytetrafluoroethylene d-PTFE.
- Titanium mesh.

b. Resorbable Membranes:

- Synthetic polymeric materials (polylactide and polyglycolide).

- Polypeptide collagen materials.
- Acellular dermal matrix

1.39.2 GBR ARP and non-resorbable membranes

Both PTFE (Lekovic et al., 1997, Becker et al., 1994b, Brugnami et al., 1996) and titanium meshes (Pinho et al., 2006) have been used either alone or in combination with a resorbable graft material (Aimetti et al., 2017, Lim et al., 2015) in ARP procedures.

PTFE is comprised of a long carbon chain with two fluorine atoms for every carbon atom. The complete fluorination of the carbon chain, along with the strength of the carbon-to-fluorine bonds, makes PTFE highly stable. This stability results in a synthetic polymer that is non-resorbable, biologically inert and chemically non-reactive. Heating PTFE and then applying a force enlarges the material's microstructure to make e-PTFE. Although this membrane has been used extensively and successfully in the oral tissues, the highly porous structure of e-PTFE allows for the ingrowth of bacteria into the defect site, when the membrane is exposed in the mouth. Exposure of the graft can result in high rates of infection and frequently requires early removal of the device. The highly porous structure can also allow soft tissue ingrowth, which may complicate its removal. It has therefore been suggested that e-PTFE barriers should be completely buried, and primary closure of the soft tissues should be achieved to ensure their predictability for ARP, limiting its role in extraction site grafting where exposure is likely (Bartee, 1998).

d-PTFE was subsequently developed with a reduced pore size of 0.3 μm, to minimise the risk of bacterial contamination and soft tissue infiltration, with the increased efficacy of membrane proven with animal and human studies (Bartee, 1995, Barber et al., 2007). Studies have demonstrated that even when the membrane is exposed to the oral cavity, bacteria is excluded by the membrane, while oxygen diffusion and transfusion of small molecules across the membrane still occur. Thus, d-PTFE membranes can result in bone regeneration even when exposed (Barber et al., 2007, Hoffmann et al., 2008). Removal of d-PTFE is also simplified due to lack of tissue ingrowth into the surface structure (Crump et al., 1996). It has been reported that d-PTFE is particularly useful when primary closure is impossible without tension, such as alveolar ridge preservation, large bone defects, and the placement of implants immediately after extraction (Bartee, 1995). In those cases, d-PTFE membranes can be left exposed and promote the preservation of the soft tissue contour and the position of the mucogingival junction. Using d-PTFE membranes can also enhance healing, as there may be no need for extensive releasing incisions to obtain primary closure, which can compromise the blood supply and cause loss of the keratinized tissue, (Bartee and Carr, 1995, Barboza et al., 2010).

Titanium re-enforced membranes has been suggested as an alternative to e-PTFE membranes, with or without the association of a grafts scaffold (Pinho et al., 2006), or in combination with a e-PTFE or d-PTFE membrane as a titanium-reinforced membrane. The embedded titanium framework allows the membrane to be shaped to fit over a variety of defects without collapsing and provides additional stability in large, non-space maintaining osseous defects. Titanium membranes are constructed to have micro-porosities small enough to prevent the penetration of cells and fibres, but which also allow the diffusion of interstitial fluid.

Whilst the barrier function of the membrane is important, there is also an important biomechanical role for the non-resorbable membrane in stabilizing and protecting the nascent clot and promoting vascularity and osteogenesis, especially in the central region of the membrane-covered bone defect (Hämmerle et al., 1995).

1.39.3 Non-resorbable membranes and dimensional and histological Changes

The application of GBR with a non-resorbable ARP membrane has shown some success.

Lekovic et al. (1997) examined the effect of using a e-PTFE barrier membrane with an ARP technique, over a 6-month period. Clinical comparison against an untreated site, demonstrated a statistically significant difference in ridge dimensions when the socket was covered with an e-PTFE barrier ($P< 0.05$). The reduced tissue resorption level was not recorded in three patients, who suffered membrane exposure.

Fotek et al. (2009) examined the effect of grafting patients with an allograft and an e-PTFE membrane. All sites were found to heal without adverse events and facilitated implant placement. Unfortunately, the e-PTFE membranes exfoliated prematurely, with an average retention time of 16.6 days. The treatment was still shown to be effective, with only a small vertical alveolar ridge hight reduction of 0.25 mm in the test group. Brugnami et al. (1996) found a similar dimensional preservation when using a combination of e-PTFE barrier and DFDBA graft matrix. Histological analysis of the ARP treated site after a 4 to 13-month healing period, revealed that although individual particles of DFDBA were still visible, they had become incorporated within new bone, without signs of inflammation or fibrous encapsulation noted around the allograft.

The option of raising a local flap, to facilitate placement of a d-PTFE membrane over the extraction socket margin was investigated by Hoffmann et al. (2008). Primary closure was not obtained over the membranes. After membrane retrieval at 12 months, non-epithelialised soft tissue was found in the membrane covered areas, with re-epithelialisation noted at 4-weeks after removal. Clinically, the whole keratinised gingiva was preserved, but a slight colour change remained. Hoffmann et al. (2008) indicated that the presence of the d-PTFE membranes promoted the preservation of the alveolar width and height, but the outcome was mainly influenced by the architecture of the existing proximal bony

walls. This feature was also noted by Lekovic et al. (1997), who indicated that the proximal bone stabilised the membrane and maintained the integrity of the GBR site.

Histologic analysis of new bone formation after using a d-PTFE membrane was reviewed by Aimetti et al. (2017). He recorded that the newly formed bone was well structured, with intense osteoblastic activity and 100% living trabecular bone. The connective tissue was free of inflammation and well vascularized in all the examined sections. The overall mean percentage of newly formed bone was found to be 49.3%± 4.7, with this tissue composed mostly of lamellar bone (33.2%±3.6). A greater percentage of mineralised bone was seen in the apical area 51.0%±6.2%.

Pinho et al. (2006) investigated the use of a titanium supported membrane alone or in combination with an autogenous graft. The study indicated that although exposure of the titanium membrane occurred in 5 of the 10 treated subjects, this did not affect the degree of preserved bone, with the preservation levels similar in both the titanium and autogenous graft group (8.80 ± 2.93 mm (range 4-13)) and where the titanium membrane was used alone (8.40 ± 3.35 mm (range 4-13)). The dimensional change of the bone width was 1.40mm ± 1.97 (range -4to -1) in the combination graft group and 1.40mm ± 0.98 (range -4to -0) in the membrane group. The use of a titanium membrane alone, or in combination with autogenous bone, favoured the preservation of the alveolar ridge after tooth extraction. Maeda et al. (2021) also demonstrated the effectiveness of an ARP procedure using an anodized titanium foil membrane and a bovine graft matrix, demonstrating preservation of the horizontal alveolar ridge at 6-months.

1.39.4 Resorbable GBR membranes

Polymeric membranes and collagen membranes have been used extensively in ARP procedures (Lekovic et al., 1997, Barboza et al., 2010, Bartee, 1998). Polymeric materials are made up of synthetic polyesters, polyglycolides (PGAs) and polylactide acid (PLA) derivatives. Collagen membranes are made using collagen materials derived principally from human acellular dermal tissue / tendons of bovine and porcine sources. These membranes are normally manufactured from Type-I collagen alone, or a combination of Type-I and Type-III collagen tissue. The membranes are created by extraction of a coagulation from a collagen solution, which is then air-dried to form plates. The degree of cross-linking of the collagen molecules determines the resorption rate of the material, with non-cross-linked membranes constructed to have an average survival time of 6 to 8 weeks in situ. This construction reduces the risk of antigenicity, with the degradation and resorption rate of the membrane, mirroring the timings of early wound healing.

The use of a collagen barrier membrane in GBR is reported as having a similar clinical efficacy as a non-resorbable polytetrafluorethylene (PTFE) membrane (Caffesse et al., 1997). It is also associated with several clinical advantages (Retzepi and Donos, 2010, Hämmerle and Jung, 2003), which include:

a) Improved haemostasis.

b) Stimulus of the chemotaxis of fibroblasts.

c) Support for the migration of fibroblasts.

d) Ease of shaping and adaptation

e) One stage to the procedure.

f) Low antigenic and immunogenic properties.

g) Predictable resorption and breakdown pattern.

Nevia 2011 performed a detailed evaluation of healing extraction sockets covered with a resorbable collagen membrane only. Histological and evaluation and CT radiography demonstrated that adequate bone formation for implant placement occurred as early as 12 weeks following tooth extraction, with minimal changes in alveolar ridge dimensions and a new mean bone percentage of 45.87% ±12.35.

Collagen membranes have excellent soft tissue healing properties, with minimal tissue reaction on exposure (Iasella et al., 2003). The healing pattern is also advantaged, by the resorbable nature of the membrane and its complete biodegradation, with this process preventing the requirement for a second surgical procedure to remove the barrier. Polymeric materials breakdown through hydrolysis, to carbon dioxide and water (Krebs cycle), a catabolic process similar to that associated with normal cellular regeneration,

The process can be rapid, (Von Arx et al., 2005) and can affect the effectiveness of the material as a physical barrier (Owens and Yukna, 2001, Gielkens et al., 2007). The possibility of early, beyond 30-days, loss of the membrane's occlusive properties, is important, as it would influence the body's ability to promote bone healing (Gielkens et al., 2007). This property may be a potential disadvantage for an ARP barrier, as exposure of the membrane to the oral environment may precipitate breakdown of the barrier integrity, influencing new bone formation (Buser et al., 1999, Machtei, 2001). The systematic review by Garcia et al. (2018) indicated that early membrane exposure in GBR procedures has a particularly detrimental influence on the outcome of bone augmentation, with sites without membrane exposure achieved 74% more horizontal bone gain than the sites with exposure. For peri-implant dehiscence defects, sites without membrane exposure had 27% more defect reduction than the sites with exposure.

Membrane integrity can be prolonged by using a double layer technique (Dubovina et al., 2020, Yun et al., 2011), or by increasing the level of cross-linking of the collagen fibres (Garcia et al., 2018, Wessing et al., 2018). A number of different physical and chemical methods have been used to increase collagen

cross-linking. These methods have included ultraviolet radiation, and treatment with chemical solutions such as genipin, glutaraldehyde, and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride. Although chemical cross-linking has resulted in improvement of collagen stability, residues of chemicals (amides or aldehydes) have been reported to induce severe inflammation at the implantation site (Zubery et al., 2008, Rothamel et al., 2004). Therefore, the predictability of the collagen membrane not only depends on the origin of the collagen material but also on the preparation and processing procedures (de-cellularization, sterilization, and method of cross-linking (Elgali et al., 2017).

Of consideration, is the finding that increased membrane integrity may causes a delay in the membranes resorption rate and reduce its permeability. This reduced permeability may decrease blood vessel formation and the level of soft tissue healing (Tal et al., 2008, Willershausen et al., 2014). Experimental findings have also suggested an active role of the membrane compartment (Calciolari et al., 2018a), in promoting the regenerative processes in the defect site during GBR procedures (Elgali et al., 2017, Omar et al., 2019, Turri et al., 2016). The evidence suggests that the GBR membrane actively promotes the recruitment of cells that migrate into the defect site, with these cells becoming associated with the membrane. Concomitantly, the membrane enables the signals from the membrane-associated cells to be communicated to cells in the underlying defect, thus creating a local environment conducive to bone formation and remodelling.

1.39.5 ARP open barrier GBR techniques

One of the major surgical considerations associated with an ARP GBR technique, is that insufficient soft tissue remains at the extraction site, to facilitate complete coverage of the exposed biomaterials in the alveolus. This deficiency leads to the requirement for tissue advancement, placement of a free gingival graft, or the use of a pedicle graft, to achieve primary tissue closure and protection of the healing site. These procedures are associated with additional patient trauma and the use of a complex surgical procedure.

Funakoshi (2007) introduced the “Open Barrier Membrane Technique” as a novel, minimally invasive ARP GBR procedure, which used a high-density d-PTFE membrane in conjunction with an autogenous bone or bone substitute. The membrane was placed on the bone surface without repositioning or advancement of the flap and sutured without periosteal releasing incisions. Primary closure was not attempted. The potential advantage of this procedure was its minimally invasive technique, simplicity of the membrane removal, reduced surgical complexity, enhanced keratinized gingival tissue formation and the ability to overfilling the socket. The results of this indicated that this technique produced a stable and predictable bone volume, with an increase in the socket height of 0.9mm. Overfill or neo-genesis of the bone was possible, as primary closure was not required. The use of an open barrier ARP GBR technique, using a resorbable membrane is now seen as a viable treatment option, reducing the

difficulty associated with the procedure (Barber et al., 2007, Choi et al., 2017, Sun et al., 2019) and has led to the development of the SS surgical protocol (Landsberg and Bichacho, 1994). Choi et al. (2017) examined the open healing approach using a single or double layered collagen membrane, reporting an alveolar width reduction of -1.7mm ±0.5 mm in the single layer group and -1.8mm ±0.4 reduction in the double layer group. Both approaches were seen as suitable for ARP. Whilst the open membrane approach would seem a practicable solution for clinicians, the risk of early membrane degradation with oral exposure membrane remains a risk. Limited data is currently available on the effectiveness of the open healing concept versus fully a submerged GBR membrane for ARP (Choi et al., 2017).

1.39.6 ARP with the combination of GBR

The combination of a graft material with a resorbable membrane is one of the most common strategies used by dental professionals in the clinical setting. The results from studies using a graft and membrane GBR approach are outlined in Tables 11 to 16. Whilst Vance et al. (2004) and Hoffmann et al. (2008) have demonstrated that ARP using a GBR technique alone can be successfully used without a bone scaffold, there is perceived to be a clinical advantage for using a combination of membrane and graft. This surgical protocol improves the stability of the graft matrix (Hürzeler et al., 1998, Blumenthal, 1993, Donos et al., 2002b), provides greater support for the membrane in the middle section of the socket (Hoffmann et al., 2008) promotes osteoconduction and reduces the risk of graft resorption (Troiano et al., 2018). Iasella et al. (2003) proposed that a gain in socket vertical bone height was only possible when a GBR technique was used in combination with a block or particulate graft, in combination with a membranes or titanium mesh.

1.39.7 Dimensional changes with the combination of GBR barrier and grafts

The effectiveness of a combination graft and membrane GBR approach to ARP has been reported by many authors. Iasella et al. (2003) demonstrated that the application of a collagen barrier membrane with FDBA, was associated with a reduction in the alveolar bone horizontal (1.3 ± 2) and vertical (-1.2mm ± 0.9) dimensions. Barone et al. (2008) found a similar reduction in the horizontal (-2.5mm ± 1.2) and vertical (-0.7mm ±1.4) alveolar remodelling rate, when augmenting the socket with a collagen membrane and a porcine xenograft matrix. Jung et al. (2013b) and Patel et al. (2013) demonstrated an effective horizontal (-1.2 mm ± 0.8 and -2.1 mm ± 1) and vertical (-1.5 mm ± 1.2 and +0.2 mm ± 0.7) reduction when using DBBM and a collagen membrane, with Aimetti 2009 and Clozza 2012, observing similar results with an alloplastic material. Poulias et al. (2013) noted a horizontal bone loss of only (-0.3mm ± 0.9), when combining a resorbable membrane with a human allograft or xenograft.

The systematic review by Avila-Ortiz et al. (2019) concluded that there was an unambiguous advantage to using an absorbable collagen membrane for GBR over a xenogenic or allogenic graft when

considering alveolar ridge horizontal contour preservation. Similarly, the meta-analysis by Troiano et al. (2018) demonstrated the superiority of the GBR technique when compared against grafting alone. This review indicated that GBR was associated with an alveolar ridge width resorption rate of 2.19 mm and vertical height change of 1.72 mm. Whilst the GBR technique was seen to be preferable to other ARP, the advantage of using GBR with a specific graft matrix was undetermined.

1.39.8 GBR histological changes with graft and membranes

Meta-analyses on histological studies have revealed less new bone formation (35% ± 16%) following the sole use grafts when compared to their combined use with a membrane (40% ± 16%) (Canellas et al., 2020, Chan et al., 2013). The systematic review by Canellas et al., 2020, indicated a -22.5% reduction in new bone formation with DBBM, a -13.3% reduction with a DBBM plus collagen graft and a -22% reduction with a FDBA graft. The histological outcomes from ARP procedures using GBR are presented in Tables 10, 12 and 14. These studies have confirmed histological evidence demonstrating bone formation around the osteoconductive graft particles as early as 3 months of healing (Carmagnola et al., 2003, Molly et al., 2008). Whilst the GBR technique demonstrates higher mineralised tissue formation than unassisted healing, it can be extrapolated that this higher percentage is due to the presence of residual graft particles. The residual graft material occupying and therefore limiting the anticipated new bone formation (Araujo et al., 2008, Canellas et al., 2020) . The reduced formation of new bone, when residual graft particles remained, has been recorded with a xenograft (Cook and Mealey, 2013, Barone et al., 2008, Perelman-Karmon et al., 2012), allograft (Iasella et al., 2003) and alloplast (Aimetti et al., 2009, Brkovic et al., 2012) graft material. Whilst new bone formation is variable but predictable, the resorption characteristics of xenograft material was also found to be unpredictable, with only partial resorption of material observed at both short and long review periods (Iasella et al., 2003, Araujo and Lindhe, 2009).

Canellas et al. (2020) advised that a xenograft was the most common material used with GBR procedures and that different categories of xenografts responded in a similar manner, despite variations in manufacturing process. Whilst the combination of xenograft & GBR techniques were effective at mitigating bone contour changes, they also resulted in a reduced level of new bone formation, with a large quantity of residual graft noted at 3-6 months healing. The clinical operator therefore needs to consider the preferential effects of soft tissue contour preservation when using ARP techniques, against the risk of reduced new bone formation and its effect on implant restorability.

1.40 Socket seal techniques

Although the application of GBR in ARP procedures has been proven to result in preservation of the alveolus and the promotion of osteogenesis at the extraction site, the procedure frequently involves complex flap manipulation that may result in undesirable side effects to the gingival tissue and a relieving incision to enable closure of the flap. This surgical requirement may deplete the blood supply to the thin labial bone plate and cause additional bone loss in the extraction site (Jung et al., 2004). The side effects include gingival marginal recession, loss of keratinized tissue, reduced interdental papillary height, reduced tissue thickness, alteration to the muco-gingival line (Engler-Hamm et al., 2011) and scarring of the soft tissues influencing the aesthetic outcome of future implant treatment (Landsberg, 2008).

The SS technique has been proposed as a simplified, minimally invasive regenerative technique, for optimising the preservation of the hard and soft tissue components of the alveolar ridge, immediately following tooth extraction (Landsberg and Bichacho, 1994). The technique proposed the use of a free gingival graft (FGG) to achieve primary tissue closure at the extraction socket, which functions as a protective seal, preventing the loss of an underlying graft (Landsberg and Bichacho, 1994). Alternatively, it can be used to promote soft tissue healing alone, augmenting the post extraction mucosa in the entrance of the socket.

The original SS procedure was described by (Landsberg and Bichacho) in 1994, with changes to the technique introduced in (1997) and (2008). The technique is now best described as follows:

- Atraumatic tooth extraction.
- De-epithelialization of the soft tissue walls with a high-speed, round, coarse diamond bur in socket entrance.
- Placement of an absorbable bone scaffold material inside the socket.
- Light condensation of the graft material.
- Preservation of a 2 to 3 mm gap in the coronal aspect of the socket.
- Harvest of a FGG from the palatal tissue.
- Stabilisation of the graft with sutures to the socket orifice under a protective base plate or pontic.

During tissue healing, the submucosa at the base of the tissue graft acts as a barrier to prevent the penetration of epithelial cells into the alveolar bone of the socket, with the graft integrating with the connective tissue layer of the gingival tissue during healing. It has been suggested that the integration of the soft tissue graft acts to promote bone regeneration, whilst preserving the dimensions of the ridge for future implant restorations (Irinakis and Tabesh, 2007). The FGG establishes a new blood supply

from, after a fibrin clot formed between the edges of the graft and the surrounding gingival tissue of the socket aperture. The revascularisation of the graft takes time to establish, resulting in necrosis and breakdown of the top layers of the epithelial surface. Under this degenerative layer, the cells from the gingival margin begins to proliferate horizontally to cover the surface of the socket. This lateral migration of cells may reach 0.5 mm per day, under ideal conditions. Usually by the fourth week the socket is covered by new soft tissue, that seals the opening (Tal, 1999). The connective tissue graft that seals the extraction site, is mainly dependent on the underlying tissue vascularisation during healing, with the underlying bone regeneration influenced by the osteogenic properties of the allograft or xenograft materials (Tal, 1999).

The healing characteristics of the FGG graft was investigated by Jung et al. (2004), one week after insertion. His study found that 64.3% of the graft area was fully integrated at this time, with 35.6% fibrous tissue and 0.1% necrotic tissue. Three weeks after surgery, the mean integrated graft surface increased to 92.3%, with 99.7% found at 6-weeks. By 6-weeks, only 0.3% of the FGG surface showed incomplete wound closure, with no fibrin or necrotic tissue present.

The ability of the SS procedure to preserve the alveolar bone and soft tissue contour, was confirmed by the case series undertaken by Mankoo (2007) and Tal (1999). It was acknowledged that the capability to maintain the dimensions of the ridge was dependant on the characteristics of the bone substitute material used (Landsberg, 2008), but the advantage of the SS technique translated into a significant benefit in the increased dimensions and improved characteristics of the keratinised tissue margin (Moghaddas et al., 2012).

Other resorbable allograft materials have now been advocated to seal the extraction opening, promoting stabilisation of the underlying blood clot and protection of the graft matrix (Bartee, 2001, Jung et al., 2004, Araujo et al., 2015). Modification of the original surgical technique has been described by (Misch et al., 1999), who proposed the use of an autologous bone harvested from the maxillary tuberosity, in conjunction with a connective tissue and periosteum graft, to seal the coronal aspect of the extraction socket. The use of a connective tissue graft was considered clinically superior to a keratinized graft, as it regenerates by blending into the surrounding attached gingival regions, producing a colour and texture that is similar to the site's original characteristics. This feature is advantageous in the anterior maxillary area, as the aesthetics of the final prosthetic structure is more important in this region. The composite graft also offers the advantage of containing an autogenous bone layer, which will promote a more rapid and predictable bone formation via osteogenesis in the extraction site (Misch, 1996).

1.40.1 SS for gingival augmentation

The requirement to augment the tissue volume or change the histological nature of the gingival tissue varies in patients and is site specific. Extraction sites, with a lack of keratinized tissue width and soft

tissue volume have been identified as area that would benefit from interventional augmentation. This is because a stable zone of fixed keratinized tissue and soft tissue thickness is considered necessary to maintain the health of the peri-implant mucosa, improve the aesthetics of the prosthetic outcome and to mitigate against the risks of gingival recession (Adell et al., 1981, Artzi et al., 1993, Schrott et al., 2009, Bühler-Frey and Burkhardt, 2008). Thoma et al., 2009, proposed, that soft tissue grafting procedures were associated with several disadvantages:

- A limitation to the amount and quality of tissue that could be harvested.
- The lack of colour and texture match to the surrounding tissue.
- A prolonged healing time.
- An increase in the overall patient's morbidity.

To overcome these limitations and disadvantages, several alternatives to a FGG have been suggested. These included acellular and cellular dermal substitutes, cultured epithelial grafts and collagen-based matrices (Griffin et al., 2006). The use of an intra-socket reactive graft and a bovine xenograft SS technique was investigated by Mardinger et al. (2009) and (2012), with the reactive soft tissue material composed of granulation tissue and long junctional epithelium. Clinical and histological results demonstrated that the reactive matrix was able to integrate into the epithelial tissue during healing, being replaced by a keratinized gingiva layer (Mardinger et al., 2009).

Collagen grafts materials have been proposed as a solution to many of the reported limitations of tissue derivative alternatives, the evidence of their suitability remains in-substantive (Postlethwaite et al., 1978, Cardaropoli et al., 2014, Jung et al., 2013a).

Mucograft® (Geistlich Pharma AG, Wolhusen, Switzerland) is a collagen-based product, which is derived from a xenogeneic origin. This collagen matrix is purported to have a haemostatic effect, promote early wound stabilisation, possess chemotactic properties to attract fibroblasts, and be semi-permeable to promote cellular and capillary regeneration (Postlethwaite et al., 1978). The matrix is made of type I and type III collagen and organized in a bilayer structure. The bi-layer structure has a compact layer facing the oral cavity, which consists of compact collagen to fulfil the cell occlusive properties and allow tissue adherence and marginal adaptation as a prerequisite for favourable wound healing. This layer has a smooth texture with appropriate elastic properties to accommodate suturing to the host mucosal margins. The second layer consists of a thick, porous collagen spongy structure, to allow tissue integration. This roughened surface is placed next to the host tissue to facilitate organization of the blood clot and promote neo-angiogenesis. Based on these favourable biological outcomes Hämmerle and Jung (2003) proposed that Mucograft® could be used as a viable graft matrix to replace an FGG, to promote an increase in the width and volume of keratinized tissue around teeth and implants.

The effect of using a bovine xenograft and a collagen matrix, as an alternative to an autogenous FGG when using a SS technique was reviewed by Jung et al. (2013b), who after 6 months of socket healing, found no statistical difference in the horizontal alveolar ridge reduction when comparing the effects of using a SS collagen and FGG ARP test group. A -1.2 mm (-17.4%) reduction was found in the collagen group and -1.4 mm (-18.1%) when using an FGG. Meloni et al. (2015) undertook a similar study examining the effects of the SS technique when using a deproteinised bovine bone and a porcine collagen matrix, or an epithelial connective tissue graft. Five months after the tooth extraction, both groups effectively reduced the level of bone resorption, with no statistically significant differences found between the two groups for conservancy of both the horizontal and vertical alveolar bone dimensional change. The use of porcine collagen matrix appeared to allow simplification of treatment, negating the need for a palatal FGG donor site.

1.40.2 SS dimensional changes

The SS technique has been investigated by several authors to determine its effectiveness in preserving the tissue contour following tooth extraction and is outlined in Table 15. The size of the vertical and horizontal bone reduction was examined by Vanhoutte et al. (2014), who reported a horizontal and vertical reduction of the alveolar process of -0.62 mm and -0.7mm at 12 weeks, when using a bovine xenograft and a connective tissue graft. The study indicated that the procedure could almost completely counteract changes to the contour of the external soft tissue profile. It was proposed that the minor changes found in the cervical region, might disappear with the development of the emergence profile of the prosthodontic tooth and SS might therefore enhance the aesthetic outcome when a tooth was replaced in the aesthetic zone. Lambert et al. (2012) also reported a significant bone preservation following SS in conjunction with a collagen seal, finding that the horizontal dimension of the alveolar ridge decreased by -1.6 mm (20%) at 2 mm below the alveolar crest, -1 mm (12%) at 5 mm and -0.5 mm (6%) at 8 mm. The losses were always significantly higher in the buccal area than in the palatal aspect. Vertical bone resorption was homogeneous and <-1 mm in the measured regions.

Table 15. *Vertical and horizontal alveolar ridge dimensional changes following SS ARP (mm)*

Author	time	Intervention	Bone width	Buccal Vertical bone height	Lingual/ palatal vertical bone height
(Fotek et al., 2009)	4m	Acellular dermal matrix+ MBA PTFE membrane	− 1.2mm ± 0.8 − 1.4mm ± 1.0	− 1.4 mm ± 1.0 − 1.4 mm ± 1.0	
(Jung et al., 2013c)	6m	Collagen matrix+ DBBM-c	− 0.1mm ± 0.2 − 0.6 mm ± 0.9	+ 0.6 mm ± 1.2 + 0.6 mm ± 1.2	
(Karaca et al., 2015)	3m	FGG only	− 0.99 mm ± 0.8	+ 0.6 mm ± 1.2	
(Meloni et al., 2015)	5m	Collagen matrix +FDBA	− 0.31 mm ± 0.18		
(Natto et al., 2017)	4m	Collagen sponge + FDBA	-1.47 mm ±1.29 -1.21mm ± 1.22	-0.79 mm ± 3.07 -0.3 mm ± 1.09	
(Schneider et al., 2014)	6m	Collagen matrix + DBBM FGG +DBBM		-1.15 mm ± 0.5 -1.16 mm ± 0.68	
(Debel et al., 2021)		DBBM and FGG DBBM and Gelatine	7.1 mm 4.0 mm 2.5 mm 4.8 mm 2.3 mm 1.3 mm	-0.8mm ± 0.6 -0.7mm ± 0.5	
(Landsberg et al., 2020)	6m	Bio-Oss® and FGG	-5.3% (Sd 13.4)		
(Maiorana et al., 2017)	6m	DBBM and Collagen Matrix	-1.21mm	-0.4mm	
Vanhoutte et al. (2014)	3m	DBBM and Connective Tissue	-0.62 mm	-0.7mm	
Lambert et al. (2012)			-1.6 mm (20%) at 2 mm -1.0 mm (12%) at 5 mm 0.5 mm (6%) at 8 mm		

Legend: DBBM, demineralise bovine bone matrix, FDBA freeze-dried bone allograft; PTFE, polytetrafluoroethylene and FGG, free gingival graft.

1.40.3 SS bone histology

Histomorphometric analysis of SS ARP sites, reveal 40%±19 (13.7% to 74.8%) new bone formation, with 25.7%±13 (0.6% to 51%) residual bovine graft and 34.3%±15 (13.8% to 71.9%) connective tissue matrix (Mardinger et al., 2009). Mucosal samples taken at implant placement demonstrated no residual granulation tissue within the keratinized mucosa layer. Maiorana et al. (2017) however found a higher level of residual particles (31.97%±3.52) in conjunction with a lower level of new bone formation (16.02%±7.06).

The histology of SS bone cores was examined by Lindhe et al. (2014), following SS augmentation using Bio-Oss® and a collagen plug. The harvested bone samples indicated that the amount of bone marrow and osteoid tissue was five times greater in an unassisted healing site, when compared to the grafted socket. The grafted socket contained 39.9% (± 8.6) new bone matrix, 32.4% (±9.2) fibrous tissue and 19.0% (±6.5) residual graft matrix. Lindhe et al. (2014) proposed that the retained Bio-Oss® was

resistant to resorption and slowed healing at the site. This delayed healing pattern was also demonstrated by Geurs et al. (2014), who investigated the difference in the bone histology following SS using FDBA, beta-TCP, FDBA/beta-TCP/PRP and FDBA/beta-TCP/PDGF grafts, in association with a collagen plug. His study concluded that the presence of bone graft suppressed new bone formation during the early stages of healing, but that all treatment modalities achieved a significant amount of additional new vital bone formation, when compared to unassisted healing. The delay in bone healing was attributed to the presence of residual graft particles (Lindhe et al., 2014).

Implant survival and success

1.41 ARP and implant placement

The loss of a tooth is often physically and psychologically traumatic, with the incentive to replace the tooth instinctive on both aesthetics and functional grounds. The success and establishment of implant supported restorations and the predictability of the osseointegrated interface (Adell et al., 1981, Albrektsson et al., 1981, Albrektsson and Sennerby, 1991) has led to their adoption as the preferred rehabilitative choice for patients. Successful osseointegration of the implant is influenced by the level of implant stability at placement (Albrektsson and Sennerby, 1991) with the varying morphometric dimensions of the bone donor site, the volume and quality of the boundary bone (Martinez et al., 2001) and degree of implant bone contact influencing osteogenesis at the interfacial margin (Misch, 2001). Osseointegration is alleged to occur more successfully with an implant that optimises contact with the alveolar bone and is firm and immovable at placement in the donor site. This steadiness or immovability has been described as its 'primary stability' and is considered paramount to successful osseointegration and implant survival (Brånemark et al., 1977, Adell et al., 1981, Lang et al., 1994, Martinez et al., 2001)

Long-term *in vivo* studies by Misch (2001), demonstrated that anatomical congruence between bone and implant fixtures produced a more predictable prognosis, with success rates for implants with a high level of implant primary stability (95%) reported by Adell et al. (1986) and Albrektsson et al. (1988). Clinical failure rates for mobile implants are reported at 32% by Friberg et al. (1991).

The clinical perception of primary stability is associated with the resistance of the implant to rotational and lateral forces during and after prosthetic placement (Friberg et al., 1999), with factors considered to influence primary stability including the quality and density of bone at the intended site (Meredith et al., 1998, Jemt and Lekholm, 1995).

ARP techniques cannot prevent the bodies physiological healing and ridge contour change after tooth extraction, but it has been observed to limit the extent to which these bone and soft tissue changes can occur (Avila-Ortiz et al., 2019). The improved bone width and height at the healed socket, has the potential to improve primary implant stability, improve interfacial bone contact and modify the composition and quality of the bone foundation (Tonetti et al., 2019). These changes have the ability to both affect the osseointegration process, but also to potentially simplify implant placement procedures (Horváth et al., 2013, Tan et al., 2012, Atieh et al., 2021) since it reduces the necessity of simultaneous guided bone regeneration (GBR) at early implant placement (4–8 weeks after tooth extraction) (Avila-Ortiz et al., 2019, Jonker et al., 2021, Thoma et al., 2020a).

Survival rates for implants placed in a grafted socket are outlined in Table 16. Tran et al. (2016) compared implant survival rates following ARP in a dental School setting over a 5- and 10-year review period. Despite a 2% and 7% reduction in survival rates for the ARP group, no statistical difference in the survival rate was found when comparing implants which were placed in native bone, or bone-grafted sites. The systematic review by Jung, examined implant survival in ARP sites, indicating a 97.2% and

95.2% survival at 5 and 10 Years. Despite these auspicious outcomes, there is still considered to be a lack of clinical evidence regarding the survival and success criteria of an implant placed in ARP sites and the influence of the grafting material on healing (Jonker et al., 2021).

Table 16. *Implant survival rates (%) following fixture placement in an ARP augmented site.*

ARP study	Survival rate	Time period
(Compton et al., 2017)	92.9%	10 years
(Howe et al., 2019)	94.6%	10 years
(Alghamdi and Jansen, 2020)	90%	10 years
(Crespi et al., 2020)	88.1%	10 Years
(Minetti et al., 2020)	98.2%	1 year

1.42 Implant survival

In order for researchers to describe the clinical status of the dental implant, different survival and success criteria have been described. The most commonly reported criteria was the survival rate. The survival rate designates whether the implant is still physically present in the mouth or whether it has been removed (ten Bruggenkate et al., 1990, Salvi and Lang, 2004). Supporters of this classification indicated that it provides the clearest presentation of the status of the implant, whilst critics arguing that it may create bias, as implants with pain or disease may be wrongfully maintained in the mouth. Survival rates for endogenous implant fixtures have been well documented in clinically controlled trials (Esposito et al., 2005), with the systematic review by Jung et al. (2012) indicating a 99% success rate at 10 year and Pjetursson et al. (2012) finding 80.1% over a 5 year observation period. Pjetursson et al. (2012) indicate that when failure occurred, it present either as an early complication after implant placement, or late failure following periods of implant stability. Late failures potentially being the result of excessive load (Isidor, 1996, Isidor, 1997) or infection such as periimplantitis (van Steenberghe et al., 1993).

Ong et al. (2008a) considered that a percentage cumulative ‘‘survival’’ rate would be a superior index, as it would indicate whether a certain percentage of implants were still present in the mouth at the end of the observation period. The observation period being classified into cumulative implant survival from placement, or from loading (post-loading survival rate). The results could also be presented as incidence of implant loss (‘‘failure’’ rate), that is the number of losses divided by the sum of lengths of time at risk for each implant.

1.43 Implant Success

Porter and von Fraunhofer (2005), undertook a comprehensive review of the predictors of dental implant success or failure, indicating that the main predictors for implant success were the quantity and quality of bone, the patient's age, the dentist's experience, location of implant placement, length of the implant, axial loading, and oral hygiene maintenance. Primary predictors of implant failure were poor bone quality, chronic periodontitis, systemic diseases, smoking, unresolved caries or infection, advanced age, implant location, short implants, acentric loading, an inadequate number of implants, parafunctional habits, and absence/loss of implant integration with hard and soft tissues (Karthik et al., 2013). Inappropriate prosthesis design was also seen as a contributing factor to failure (Alghamdi and Jansen, 2020). Whilst these predictors are important in assessing and planning implant treatment, and restricting risks associated with failure, they do not provide a framework to review implant survival characteristics (Salvi and Lang, 2004). It was also considered important that studies report on implants after at least 6 months post-loading, to allow biological complications during function to be observed, rather than early implant failures (Heitz-Mayfield et al., 2020).

Multiple studies have examined the criteria for implant success, with Schnitman and Shulman (1979) defining success as mobility of less than 1 mm in any direction, the absence of implant radiolucency’s, bone loss no greater than one third of the vertical height of the bone, gingival inflammation amenable for treatment and functional service for more that 5 years in 75% of patients.

Cranin et al. (1982) required the implant to be in place for more than 60 months or more, lacking evidence of cervical bone loss or widening of the peri-implant space on radiographs and the absence of bleeding, mobility and pain or percussive tenderness at the implant site. The health of the peri-implant mucosa tissue was also considered.

McKinney et al. (1984) defined implant success according to subjective, objective and success criterion, requiring functional endurance of over 75% after 5 years’ service, with the criteria for success outlined according to implant mobility, peri-implant radiolucency and margin bone loss possible. Patient beliefs and aesthetic and psychological factors were also included in the assessment. Adell et al. (1986) determined that the mean bone loss for Brånemark osseointegrated implants was 1.5 mm for the first year, followed by mean bone loss of 0.1 mm/year. This observation resulted in Smith and Zarb (1989)

determining that a mean bone loss of less than 0.2 mm per year, was a preferred criterion for success. While other classifications of implant success have been discussed, the classification by Albrektsson et al. (1986) has been used as the basis for most recent implant investigative studies.

Albrektsson et al. (1986) outlined his criteria as follows:

1. Individual unattached implant that is immobile when tested clinically
2. Radiography that does not demonstrate evidence of peri-implant radiolucency
3. Bone loss that is less than 0.2 mm annually after the implant′s first year of service
4. No persistent pain, discomfort, or infection
5. A success rate of 85% at the end of a 5 year observation period and 80% at the end of a 10 year period are minimum levels for success.

However, the classification proposed by Albrektsson et al. (1986), did not take into consideration the amount of crestal bone lost during the first year of healing and the scenario where a patient could suffer an initial phase of bone loss, before establishing a stable condition in the mouth

In response to these observations, Buser et al. (1990) proposed an update of this classification, defining the following criteria: (1) absence of persistent symptoms such as pain, sensation of foreign body and/or dysesthesia, (2) absence of recurrent peri-implant infection with suppuration, (3) no mobility, (4) absence of peri-implant radiolucency and (5) feasibility of restoration.

Karoussis et al. (2003) also expanded upon Albrektsson et al. (1986) proposal, adding in two additional implant success parameters, PPD≤5mm and the absence of bleeding on probing with a PPD of 5mm.

In 2008, at the International Congress of Oral Implantologists, Misch et al. (2008) set out to define implant success, survival, and failure. He modified the James–Misch Health Scale and outlined 4 clinical categories, with supplementary conditions for implant success, survival, and failure. Implant success was defined as no pain or tenderness upon function, absence of mobility, <2 mm radiographic bone loss from the initial surgery and no presence of exudate. The classification also proposed including an assessment time of at least 12 months for implants serving as prosthetic abutment and a separate prosthetic survival report.

A more comprehensive evaluation of the criteria of implant success was defined by Papaspyridakos et al. (2012), who recommended reporting on success at different levels: implant, peri-implant soft tissue, prosthetic and patient.

Ong et al. (2008) indicated that there was a lack of consensus regarding a set of universally accepted success criteria, designing a systematic review to assess all past definitions of implant success. All

levels of bone change were considered, with both clinical and radiographic criteria examined to define success. Emphasis was also given to the signs and symptoms of peri-implantitis (Heitz-Mayfield et al., 2020) as outlined by (Albrektsson et al., 1986) and adapted by (Buser et al., 1990) and Karoussis et al. (2003)

Ong et al. (2008) identified 7 different criteria for implant success outlining the criterion as follows:

1. Absence of mobility (Buser et al.1990).
2. Absence of persistent subjective complaints (pain, foreign-body sensation and/or dysaesthesia) (Buser et al. 1990).
3. Absence of recurrent peri-implant infection with suppuration (Buser et al. 1990).
4. Absence of a continuous radiolucency around the implant (Buser et al. 1990).
5. No pocket probing depth (PPD)> 5mm (Mombelli and Lang, 1994, Brägger et al., 2001).
6. No PPD > or =5mm and bleeding on probing (BOP) (Mombelli & Lang1994).
7. After the first year of service, the annual vertical bone loss should not exceed 0.2mm (mesially or distally) (Albrektsson et al. 1986 and Albrektsson & Isidor 1994).

1.44 Requirement for bone augmentation

Recently, studies have begun to explore whether additional augmentation was needed at the time of dental implant placement, following an ARP procedure (Avila-Ortiz et al., 2019, Barone et al., 2013a). The RCT undertaken by Avila-Ortiz et al. (2020b) indicated that bone augmentation was necessary in 48.1% of unassisted healing sites and only 11.5% of the ARP sites, to facilitate implant placement in a prosthetically acceptable position. The systematic review by Horváth et al. (2013), found that only limited evidence was available to support the clinical benefit of ARP. Namely, a reduced need for further augmentation in conjunction with dental implant placement. Atieh et al. (2021) also examined ARP and the requirement for additional grafting of the ARP site. The review indicated that whilst the techniques may minimise the overall changes in residual ridge height and width at six months healing, there lacked strong evidence of any differences in the need for additional augmentation at the time of implant placement. The heterogeneity in the literature, indicates that there is still a need for sound clinical evidence to link ARP with a simpler implant placement surgical protocol.

PhD Study Design

1.45 Aims of the PhD thesis

Failure to achieve an adequate or stable peri-implant architecture of bone and soft tissue, has been recorded as adversely influencing implant survival characteristics (Seibert and Salama, 1996), as it increases the risk of subsequent bone and gingival tissue loss (Artzi et al., 1993) and negatively influences the design and aesthetics of the prosthetic tooth replacement (Pagni et al., 2012, Chen and Buser, 2009, Kois, 2004).

The effects of varying the timing of implant placement following tooth extraction, have also been examined (Chen and Buser, 2009, Esposito et al., 1998, Hammerle et al., 2012b, Sanz et al., 2012, Fugazzotto, 2005). The timing of implant placement is considered important, as immediate, or early surgical intervention may help to reduce the degree of tissue remodelling, shorten the treatment time for the patient and allow sufficient soft tissue regeneration to facilitate local grafting procedures to be undertaken at the time of implant placement. However, the adoption of an early implant placement protocol may limit the availability of alveolar bone at the osteotomy site, affecting the ability to achieve adequate primary stability of the implant fixture, increasing the requirement for additional bone augmentation during the surgery. It may also increase the risk of osteomyelitis (Takeshita et al., 1997, Rosenquist and Grenthe, 1996), due to inadequate resolution of past local pathology and necessitate the advancement of the peripheral soft tissue to promote effective guided tissue healing. Alternatively, the lack of available alveolar bone and gingival tissue, may necessitate the adoption of a delayed implant placement protocol (Rosenquist and Ahmed 2000). Immediate or early implant placement techniques are also recognised as being linked with a risk of continuation of the remodelling process, potentially leading to a compromise in the final aesthetic outcome ((Kan et al., 2007, Chen and Buser, 2009, Sanz et al., 2012)) as a result of unplanned soft tissue and bone changes.

To reduce the negative implications associated with physiological healing and to promote an optimal bone and gingival tissue foundation for a successful implant supported restoration, investigators have sought to adapt the remodelling process by directing or guiding the tissue regeneration using augmentation or regeneration techniques. These techniques have included ARP procedures (Horváth et al., 2013, Tan et al., 2012, Darby et al., 2009), soft tissue grafting techniques and transitional prosthodontic processes (Vittorini Orgeas et al., 2013). Alternatively, clinicians have accepted the initial bone resorption changes, with development of the bone site; through Guided Tissue Regeneration (GTR) or GBR at the time of implant placement (European Osteology Guidelines 2014) (Tonetti and Hammerle, 2008). Both options are recognised as having the ability to produce a healthy bone profile compatible with successful implant osseointegration (Mardas et al., 2015).

Direct grafting and augmentation of the extraction socket has been proposed using autogenous bone (Becker et al., 1996), demineralized freeze-dried bone allograft (Becker et al., 1994a, Becker et al., 1996, Froum et al., 2002b), mineralized freeze-dried bone allograft (Feuille et al., 2003, Wood and Mealey, 2012), xenografts (Artzi et al., 2000, Artzi et al., 2001, Mardas et al., 2011, Mardas et al.,

2010), alloplastic polymers (Gross, 1995, Haris et al., 1998, Serino et al., 2003, Serino et al., 2008), bioactive glasses (Froum et al., 2002b, Roriz et al., 2010) and composite ceramic materials (Mardas et al., 2010). Although these bone substitutes have been described as being able to maintain the tissue contours in extraction sites, the quantity and the quality of the replacement bone tissue has been variable, with operators reporting a further requirement to provide additional bone and soft tissue augmentation at implant placement (Horváth et al., 2013, Tan et al., 2012, Mardas et al., 2015).

Modification and augmentation of the gingival tissue at the extraction socket has also been proposed. These techniques have included GBR and grafting of the site using autogenous connective tissues, cellular and cellular dermal substitutes, mucosa equivalents, cultured epithelial grafts and collagen-based matrices. Although collagen graft materials have been proposed as a solution to many of the limitations reported for tissue derivative alternatives, the evidence of their suitability remains in-substantive ((Postlethwaite et al., 1978, Cardaropoli et al., 2014).

Heterogeneity exists in the published data regarding the clinical, dimensional and histological outcomes following ARP. This variation in results has led researchers (Vignoletti et al., 2012, Horváth et al., 2013, Avila-Ortiz et al., 2014a, Vittorini Orgeas et al., 2013, Postlethwaite et al., 1978, Cardaropoli et al., 2014, Jung et al., 2013b) to conclude that further research was required to develop a clearer understanding of the variability and characteristics of the clinical outcomes attributed to each ARP grafting procedure. Recommendations outlined a need for future studies to be focus on investigating a small group of precise and well documented surgical techniques, testing a limited amount of graft materials and barriers, and considering the primary role of the biologic principles of wound healing. This clarification should provide a clearer understanding of the outcome of ARP techniques, detailing vertical and horizontal radiographic changes, dimensional or contour changes in the proximal and mid-socket area, the effect on bone and soft tissue healing, histological outcomes and implant success (Atieh et al., 2012). The research should guide clinical operators, advocating the advantages of alternative ARP treatment modalities.

The findings of the 4th European Association of Osseointegration (EAO) consensus conference (Sanz et al., 2015) and the Systematic Review by (Horváth et al., 2013) concluded that a lack of consensus was present regarding the impact of ARP on:

a) The radiographic dimensional changes, when undertaking ARP using either a GBR or SS techniques.
b) The ability to place an implant fixture in an extraction socket, according to prosthetic protocol.
c) The need for additional bone augmentation, at the time of implant placement.
d) Success and survival characteristics of implant placement.
e) The degree of soft tissue contour change.

f) The effect on bone and soft tissue healing characteristics.
g) The histological bone composition of the socket after 4 months healing.
h) Patient-based outcome measures, including pain and surgical complications.

1.46 Objectives of the PhD Thesis

The structure of the PhD thesis was designed to investigate these key areas and to provide clinicians with additional evidence and outcome data to guide their decision making. The investigation was configured into three main projects:

a) A Systematic Review on Implant Outcomes Following ARP

An examination and meta-analysis of preclinical and clinical studies, to evaluate the effect of ARP on implant outcomes when compared with unassisted socket. Outcomes to investigate included socket healing and its effect on implant placement feasibility, the need for further bone augmentation, implant survival/success rates and marginal bone loss.

An estimate of the size effects of these outcomes would be calculated, following ARP with GBR, socket grafting and SS techniques.

b) A Systematic Review of Clinical Based Outcomes Following ARP

An examination and meta-analysis of the effects of ARP on linear and volumetric alveolar socket dimensions, keratinised tissue measurements, histological characteristics and patient-based outcomes, when compared to unassisted socket healing.

An estimate of the size effects of these outcomes would be calculated following ARP with GBR, socket grafting and SS techniques.

c) An Independent Randomised Controlled Trial (RCT):

To compare the clinical and patient-based outcomes following ARP using a GBR versus SS technique. The control for the trial would be an unassisted socket healing site. The test groups and control sites would be planned for implant placement at 4 months (Type-3 implant placement).

Primary Outcome Measure

The change in the radiographic vertical dimensions of the buccal and palatal alveolar crest, following ARP using a SS or GBR technique when compared with unassisted healing. Dimensional change was recorded at the baseline of tooth extraction and following 4-month

healing.

Secondary Outcome Measures

Secondary outcome measures were split into five investigative domains:

Radiographic Alveolar Bone Dimensional Changes

a. The horizontal radiographic bone dimensional change.
b. Radiographic mid-socket and alveolar process, cross-sectional area changes.
c. The thickness of the buccal socket wall after tooth extraction.

Patient Outcome Measures

a. Pain scores during the first month of healing.

Healing complications at the extraction socket following ARP or unassisted healing.

Soft Tissue Contour Changes and Healing Characteristics

a. Horizontal and vertical tissue healing contour changes.
b. Magnitude of mucosal contour change
c. The width of the keratinised tissue.
d. Soft tissue characteristics after socket healing.
e. Mucosal thickness

Histological Bone Composition After Socket Healing

a. Bone healing characteristics (new bone / connective tissue / residual graft).

Implant Success

a) Implant placement feasibility.
b) The requirement for additional bone augmentation at implant placement (4 months).
c) Implant success and survival rates.

Tissue changes were recorded at baseline, immediately following tooth extraction and following 8 weeks and 4 months healing. Intra-oral clinical parameters including full mouth bleeding (FMBS) and plaque scores (FMPS). Probing pocket depths (PPD) were also be recorded.

The study will be based on the following "***Null hypothesis***": There is no difference in the alveolar bone dimensions and healing characteristics when unassisted healing is compared with ARP at a tooth extraction site.

Chapter 2

Does Ridge Preservation Following Tooth Extraction Improve Implant Treatment Outcomes: A Systematic Review

2.1 Background and aims

ARP involves any procedure developed to eliminate or limit the negative effect of post extraction resorption, maintaining the soft and hard tissue contour of the ridge and facilitating implant placement (Horváth et al., 2013). Different types of procedures have been described in the literature, including GBR, socket grafting and SS techniques.

Various grafting materials have been utilised individually or in combination with resorbable (Iasella et al., 2003, Barone et al., 2008, Mardas et al., 2010) or non-resorbable GBR barriers (Lekovic et al., 1997) to reduce the post-extraction remodelling effect. Previous systematic reviews and consensus papers have concluded that, although ridge resorption was not prevented following ARP procedures, the procedure was effective at reducing the extent of tissue remodelling after bone and soft tissue healing. The resultant bone contour being also compatible with the formation of a bone surface, able to facilitate implant fixture placement (Horváth et al., 2013, Vignoletti et al., 2012, Wang and Lang, 2012, De Risi et al., 2015, Morjaria et al., 2014, Avila-Ortiz et al., 2014a). There remains however, a lack of consensus whether ARP directly improves implant related outcomes, such as implant placement feasibility, need for additional augmentation during implant placement, the survival and success rates of implants placed in ARP sites and the marginal bone loss of implants, when compared to fixtures placed in unassisted healing sites. As no specific graft matrix or interventional ARP technique has been associated with a superior implant outcome (Horváth et al., 2013), the aim of this systematic review and meta-analysis was to investigate the additional effect of ARP on implant related outcomes, when compared to unassisted socket healing. An estimate of the effects size of outcomes was calculated according to the different ARP interventional techniques.

2.2 Study protocol

The protocol for this systematic review was developed according to the Cochrane and European Association of Osseointegration requirements for a consensus report. All investigations within this thesis were undertaken after critical analysis of human studies. Two focused questions were utilised within the structure of the report:

- **Focused Question-1**

This was considered the main question of the review, it asked:

"Is there any additional benefit of alveolar ridge preservation techniques over unassisted healing in terms of: (i) implant placement feasibility (ii) need for further augmentation (iii) implant survival, (iv) implant success and (v) marginal bone loss?"

Only longitudinal prospective studies, associated with RCTs and CCTs with unassisted socket healing as a control group, were included in the meta-analysis for this question.

- **Focused Question-2**

In order to examine data published in controlled clinical studies, where different ARP procedures had been compared, or data on case series published without a control group, the systematic review addressed a second focused question:

"What are the average incidences of implant placement feasibility, need for further augmentation and the survival, success and marginal bone loss of implants placed following different alveolar ridge preservation techniques?"

In addition to the previous studies, RCTs, CCTs and large prospective case series, without an unassisted healing control group, were included in this aspect of the meta-analysis.

2.3 Methodology

2.3.1 Population for included studies

Healthy individuals, without any age limit, who underwent any type of ARP following permanent tooth extraction with the aim of facilitating future implant placement, were included.

Inclusion criteria:

a) Studies on healthy individuals, without any age limit, who underwent ARP following tooth extraction in order to receive implants.
b) Studies providing information regarding feasibility of implant placement and/or the need for further augmentation during implant placement and/or reporting survival/success and/or proximal bone loss around the implants placed in extraction sites treated with ARP.

Exclusion criteria:

a) Retrospective studies.
b) Studies on medically compromised patients or under specific medication.
c) Studies reporting on immediate implant placement.
d) Studies reporting solely on third molars extractions.
e) Publications reporting data on the same sample and procedures as other publications.

2.3.2 Types of intervention examined

Studies examined within the systematic review, reported on ARP interventions associated with:

a) Socket grafting with various bone grafts, substitutes, or biologically active materials (growth factors).
b) SS with soft tissue grafts of different origins.
c) GBR associated with barrier membranes and combinations of grafting materials.

The minimum number of subjects per group, required for the inclusion of a controlled clinical study was 10. The number of patients required for the inclusion of case series was 20. Studies included in **Focused Question-1** compared ARP procedures with an unassisted socket healing following atraumatic tooth extraction.

2.3.3 Outcome variables

For both focused questions, four dichotomous (yes/no) and one continuous implant related outcome variable was evaluated:

a) ***Feasibility of implant placement:*** expressed as a % of implants placed with satisfactory primary stability.
b) ***The need for further augmentation*****:** expressed as a % of implants that required further bone augmentation procedures during implant placement for the management of residual dehiscence or fenestration defects.
c) ***Implant survival:*** expressed as the % of loaded and functional implants present in the arch after 12 months of loading.
d) ***Implant success:*** expressed as the % of successful implants at 12 months after loading based on specified sets of success criteria.
e) ***Marginal bone levels*****:** average of mesial and distal proximal bone loss at 12 months after loading. If mesial and distal measurements were presented but no average was provided, the mesial measurement was used for the analysis.

2.3.4 Risk of bias and methodological quality assessment

A modification of the Cochrane tool for evaluating risk of bias (Higgins et al., 2003, Higgins and Altman, 2008) was used to evaluate the methodological quality within the included studies.
The following six parameters: allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias were evaluated as being associated with a low risk, unclear risk, or high risk of bias. If all the parameters

were judged as low, the study was considered as having a low risk of bias. If at least one parameter was judged as unclear or as high risk of bias, the studies were classified as having unclear or high risk of bias respectively.

2.3.5 Search Strategy

The search strategy incorporated both electronic and hand searches, with the following electronic databases interrogated:

a) MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE 1950 to present via Ovid interface
b) EMBASE Classic + EMBASE 1947 to present via Ovid interface
c) The Cochrane Central Register of Controlled Trials (CENTRAL)
d) LILACS
e) Web of Science.

The electronic search strategy included terms related to the intervention and used the following combination of key words and MeSH terms for the different electronic databases:

Ovid Medline

1. ((tooth or teeth) adj3 extract*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

2. socket*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

3. ridge*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

4. alveo*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

5. crest*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

6. ((tooth or teeth) adj3 remov*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

7. exp Tooth Socket/

8. exp Alveolar Bone Loss/

9. exp Bone Resorption/

10. exp Tooth Extraction/

11. exp Bone Remodelling/

12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

13. preserv*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

14. reconstruct*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

15. augment*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

16. fill*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

17. seal*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

18. graft*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

19. repair*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

20. exp Alveolar Ridge Augmentation/

21. exp Bone Regeneration/

22. exp Bone Substitutes/

23. exp Transplantation, Autologous/ or exp Transplantation/ or exp Transplantation, Heterologous/ or exp Transplantation Conditioning/

24. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23

25. 12 and 24

26. randomized controlled trial.pt.

27. controlled clinical trial.pt.

28. trial.ab.

29. placebo.ab.

30. groups.ab.

31. randomly.ab.

32. drug therapy.fs.

33. 26 or 27 or 28 or 29 or 30 or 31 or 32

34. 25 and 33

35. (prospective adj3 (case or cohort or clinical)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

36. 33 or 35

37. 25 and 36

38. limit 37 to animals

39. 37 not 38

Ovid Embase

1. ((tooth or teeth) adj3 (extract* or remov*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

2. socket*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

3. ridge*.mp.

4. alveo*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

5. crest*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

6. exp tooth socket/

7. exp alveolar bone loss/

8. osteolysis/

9. exp tooth extraction/

10. bone remodelling/

11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12. preserv*.mp.

13. reconstruct*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

14. augment*.mp.

15. fill*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

16. graft*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

17. repair*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

18. exp bone regeneration/

19. (bone and (regen* or substit*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

20. exp bone prosthesis/

21. exp transplantation/

22. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21

23. 11 and 22

24. (random* adj3 (clinic* or trial*)).ab.

25. (control adj2 group).ab.

26. placeb*.ab.

27. (prospective and (case or clinical)).ab.

28. 24 or 25 or 26 or 27

29. exp controlled clinical trial/

30. exp prospective study/

31. 24 or 25 or 26 or 27 or 28 or 29 or 30

32. limit 23 to (clinical trial or randomized controlled trial or phase 2 clinical trial or phase 3 clinical trial)

33. 23 and 31

34. 32 or 33

35. limit 34 to (amphibia or ape or bird or cat or cattle or chicken or dog or "ducks and geese" or fish or "frogs and toads" or goat or guinea pig or "hamsters and gerbils" or horse or monkey or mouse or "pigeons and doves" or "rabbits and hares" or rat or reptile or sheep or swine)

36. 34 not 35

Cochrane Library, LILACS and Web of Science

#1 (tooth or teeth) and (extract* or remov*):ti,ab,kw or "socket" or "ridge" and "alveolar" and "crest" (Word variations have been searched)

#2 MeSH descriptor: [Alveolar Bone Loss] explode all trees

#3 MeSH descriptor: [Tooth Socket] explode all trees

#4 MeSH descriptor: [Bone Resorption] explode all trees

#5 MeSH descriptor: [Tooth Extraction] explode all trees

#6 MeSH descriptor: [Bone Remodeling] explode all trees

#7 preserve or recontruct or augment or fill or seal or graft or repair

#8 MeSH descriptor: [Alveolar Ridge Augmentation] explode all trees

#9 MeSH descriptor: [Bone Regeneration] explode all trees

#10 MeSH descriptor: [Bone Substitutes] explode all trees

#11 MeSH descriptor: [Transplantation] explode all trees

#12 #1 or #2 or #3 or #4 or #5 or #6

#13 #7 or #8 or #9 or #10 or #11

#14 #12 and #13

An extensive hand search was also performed encompassing the bibliographies of the included papers and other narrative and systematic reviews. In addition, the following dental journals were screened from 2001 to July 2014: Clinical Oral Implants Research, Clinical Implant Dentistry and Related Research, European Journal of Oral Implantology, Implant Dentistry, International Journal of Oral and Maxillofacial Implants, International Journal of Periodontics and Restorative Dentistry, Journal of Clinical Periodontology, Journal of Dental Research, Journal of Oral and Maxillofacial Surgery, Journal of Periodontology, Oral Surgery, Oral Medicine, Oral Radiology, Oral Pathology and Endodontics.

No language restrictions were applied, and translations were carried out if necessary. Unpublished trials and abstracts were not included in the search process. When the results of a study were presented in several publications, the most complete dataset was included in the analysis. In case of missing or incomplete data, the authors were contacted via email allowing a period of 3 weeks for their reply with the missing data.

The extracted data was copied into EndNote X8 software (Thomson Reuters, New York, NY, USA) and all further steps of screening were performed on this interface.

A three-stage selection of the resulted hits was performed independently and in duplicate by two reviewers (Dr Anna Trullenque-Eriksson and Dr Neil MacBeth). In order to reduce errors and bias, a calibration exercise was performed with the first 24 articles identified from the journal hand searched. In case of disagreement at the title selection stage, the trial was included in the abstract stage. At the abstract and full text selection, any disagreements between the above reviewers was resolved by discussion with a third reviewer (Dr Nikos Mardas). The reasons for exclusion were recorded in a specific data extraction form at the full text selection stage. The level of agreement was determined by a Kappa score calculation of agreement during the title and abstract selection process.

2.4 Research synthesis and meta-analysis

For all included studies answering both focused questions, a descriptive synthesis was undertaken. The studies were classified according to research design and type of intervention and the outcomes were recorded in evidence tables.

For **Focused Question-1**, meta-analysis was conducted utilising the available data from the RCTs and CCTs using a parallel design with the patient as unit of analysis.

For **Focused Question-2**, meta-analysis was conducted utilising the available data from all the studies included in the meta-analysis of focused question 1 and data from RCTs and CCTs without unassisted socket healing as control group, as well as larger prospective case series, as long as they used a parallel design with the patient as unit of analysis. The studies included for meta-analysis were divided into

three different interventional groups (*GBR,* socket grafting and SS). When ARP was performed utilising a resorbable or non-resorbable barrier with or without bone grafting, the study was categorised in the *GBR* group. When the socket was treated just with a graft including collagen sponges / plaques the study was categorised in the socket grafting group. Finally, the study was categorised in the SS group when a soft tissue graft or collagen layer was used to seal the entrance of the socket with or without grafting of the socket following a flapless approach.

2.5 Statistical analysis

MedCalc® Version 14.12.0, MedCalc Software bvba, Ostend Belgium) software was used for the meta-analysis relating to binary outcome variables in relation to both focused questions, and the continuous variable for focused question 1. Assessment of statistical heterogeneity was performed using Cochran's Q-test and determination of the I^2 index (Higgins et al., 2003). The I^2 index provides an estimate of the amount of variation attributable to heterogeneity (I^2 = 25%: low; I^2= 50%: moderate; I^2= 75%: high heterogeneity). The different outcome variable estimates were pooled using a fixed effects analysis if non-significant statistical heterogeneity was detected between studies. If there was evidence of statistical heterogeneity, a random effects model was used. Depending on the type of variable, different pooled estimates were provided.

For **Focused Question-1** this included:

a) Relative risk for dichotomous variables (e.g., need for further augmentation).
b) Standardised mean difference (i.e., the difference in means divided by the standard deviation) for the continuous variable (e.g., marginal bone loss in mm).

For **Focused Question-2** this included:

a) Proportion of positive responses for dichotomous variables (incidence). This figure was obtained by back transformation after taking the arcsine square root transformation of each proportion (Freeman and Tukey, 1950).
b) Mean implant proximal bone loss (mm) for the continuous variable.

Forest Plots were created to illustrate the effects of the different studies, shown against the global estimate. Statistical significance was achieved if $p < 0.05$.

2.6 Results

2.6.1 Study selection

The initial search yielded a total 14,399 records including 72 papers that were selected through hand search and one more through cross reference. After removal of duplicates and the title and abstract screening, a total of 103 articles were left for full-text assessment (*Fig. 5*). The authors of 34 out of these 103 articles were contacted at this stage in order to provide additional data on implant outcomes before the final selection. Ten papers (Iasella et al., 2003, Serino et al., 2003, Crespi et al., 2009b, Crespi et al., 2009a, Barone et al., 2012, Sisti et al., 2012, Festa et al., 2013, Barone et al., 2013a, Cardaropoli et al., 2014, Spinato et al., 2014) were eligible for inclusion in the qualitative analysis for focused question 1. The most common reason for exclusion for this focused question was the lack of control group with unassisted socket healing; insufficient number of patients; and not reporting on implants outcomes or not intending for implant placement.

Thirty studies (Serino et al., 2003, Vance et al., 2004, Neiva et al., 2008, Crespi et al., 2009b, Crespi et al., 2009a, Crespi et al., 2011a, Crespi et al., 2011b, Hoang and Mealey, 2012, Cook and Mealey, 2013, Beck and Mealey, 2010, Barone et al., 2012, Gholami et al., 2012, Mardinger et al., 2012, Perelman-Karmon et al., 2012, Sisti et al., 2012, Wood and Mealey, 2012, Barone et al., 2013a, Barone et al., 2013b, Leblebicioglu et al., 2013, Patel et al., 2013, Poulias et al., 2013, Festa et al., 2013, Wallace et al., 2013, Barone et al., 2013c, Cardaropoli et al., 2014, Coomes et al., 2013, Eskow and Mealey, 2014, Lindhe et al., 2014, Spinato et al., 2014, Iasella et al., 2003) were included in the qualitative analysis for focused question 2. The most common reason for exclusion for this focused question was insufficient number of patients; not reporting on implants outcomes; or not intending for implant placement; and duplicate reports. Several articles were excluded for more than one reason. The excluded papers and the reasons for exclusion for both focused questions are listed in Table 17.

The Kappa score for agreement between the reviewers Dr Anna Trullenque-Eriksson and Dr Neil MacBeth at the title and abstract selection level was 0.94, indicating a high level of agreement.

Figure 5: *Selection process and search strategy flowchart*

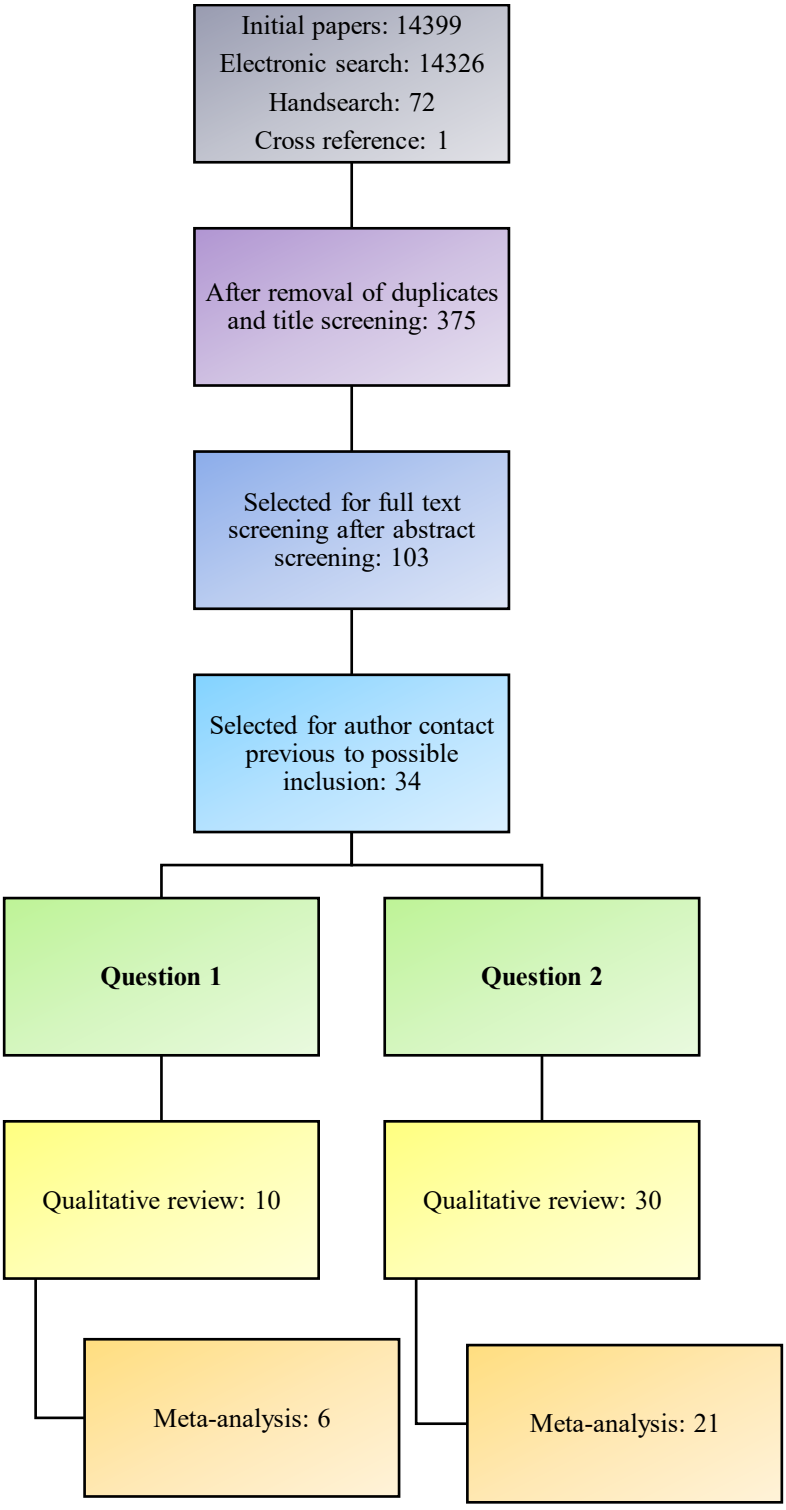


TABLE 17: *List of Excluded Papers and Reasons for Exclusion Following Full Text Screening*

Author and year	Reasons for exclusion
(Aimetti et al., 2009)	Excluded due to no relevant outcome measures being provided
(Alkan et al., 2013)	Insufficient number of patients
(Al-Khaldi et al., 2011)	Not ARP
(Anitua, 1999)	Insufficient number of patients
(Artzi et al., 2000)	Insufficient number of patients
(Babbush, 2003)	Insufficient number of patients
(Barone et al., 2008)	Duplicate report (Barone 2012)
(Brkovic et al., 2012)	Insufficient number of patients
(Brownfield and Weltman, 2012)	Insufficient number of patients
(Camargo et al., 2000)	Not reporting on implants
(Canullo et al., 2013)	Insufficient number of patients
(Canuto et al., 2013)	Not reporting on implants
(Cardaropoli et al., 2012)	Duplicate report (Cardaropoli et al. 2014)
(Carmagnola et al., 2003)	Insufficient number of patients
(Casado et al., 2010)	(Casado et al., 2010)Not reporting on implants
(Clozza et al., 2012)	Duplicate report (Clozza et al. 2014), insufficient number of patients
(Clozza et al., 2014)	Insufficient number of patients
(Collins et al., 2014)	Insufficient number of patients
(De Coster et al., 2011)	Not all patients/sockets intended for implant placement
(Engler-Hamm et al., 2011)	Insufficient number of patients, not all patients/sockets intended for implant placement
(Farina et al., 2013)	Early implant placement
(Fernandes et al., 2011)	Not all patients/sockets intended for implant placement
(Fiorellini et al., 2005)	Not reporting on implants
(Fotek et al., 2009)	Insufficient number of patients
(Geffre et al., 2010)	Animal study
(Geurs et al., 2014)	Insufficient number of patients, not reporting on implants
(Hanser and Khoury, 2014)	Study seems to be retrospective
(Hauser et al., 2013)	Insufficient number of patients
(Heberer et al., 2008)	Early implant placement
(Heberer et al., 2011)	Insufficient number of patients
(Heberer et al., 2012)	Early implant placement
(Hernandez-Alfaro et al., 2005)	Insufficient number of patients, reports on a mixture of clinical situations (ARP, discrepancy implant-socket, reconstruction after removal of implants, etc.)
(Hsuan-Yu et al., 2012)	Number of patients
(Huh et al., 2011)	Not reporting on implants
(Irinakis, 2006)	Review

(Jung et al., 2004)	Not reporting on implants
(Jung et al., 2013a)	Not all patients/sockets intended for implant placement
(Kim et al., 2011a)	Not all patients/sockets intended for implant placement
(Kim et al., 2013)	Insufficient number of patients
(Kim et al., 2014)	Not reporting on implants
(Kotsakis et al., 2014a)	Insufficient number of patients
(Kotsakis et al., 2014b)	Not all patients/sockets intended for implant placement
(Lambert et al., 2012)	Insufficient number of patients, not all patients/sockets intended for implant placement
(Lekovic et al., 1998)	Not reporting on implants
(Luczyszyn et al., 2005)	Not reporting on implants
(Madan et al., 2014)	Insufficient number of patients
(Mahesh et al., 2012)	Not reporting on implants
(Mardas et al., 2010)	Duplicate report (Patel 2013)
(Mardas et al., 2011)	Duplicate report (Patel 2013)
(Mardinger et al., 2009)	Duplicate report (Mardinger 2012)
(Misch, 2010)	Insufficient number of patients
(Moghaddas et al., 2012)	Insufficient number of patients
(Nam et al., 2011)	Not all patients/sockets intended for implant placement
(Neiva et al., 2011)	Insufficient number of patients
(Nevins et al., 2014a)	Insufficient number of patients
(Norton and Wilson, 2002)	Insufficient number of patients
(Oghli and Steveling, 2010)	Not reporting on implants
(Pellegrini et al., 2014)	Insufficient number of patients, not reporting on implants
(Pinho et al., 2006)	Not reporting on implants
(Ruga et al., 2011)	Not all patients/sockets intended for implant placement
(Scheyer et al., 2012)	Insufficient number of patients
(Schneider et al., 2014)	Not reporting on implants
(Serino et al., 2008)	Insufficient number of patients
(Simon et al., 2011)	Excluded due to no relevant outcome measures being provided
(Shakibaie, 2013)	Insufficient number of patients
(Suttapreyasri and Leepong, 2013)	Insufficient number of patients, not reporting on implants
(Tal, 1999)	Not reporting on implants
(Thalmair et al., 2013)	Insufficient number of patients, not reporting on implants
(Toloue et al., 2012)	Not reporting on implants
(Vanhoutte et al., 2014)	Duplicate report (Lambert 2012), not all patients/sockets intended for implant placement
(Villanueva-Alcojol et al., 2013)	Insufficient number of patients
(Weiss et al., 2007)	Not reporting on implants

(Wu et al., 2014)	Not reporting on implants

2.6.2 Study design and population

The study design and study population characteristics of the included studies for both focused questions are presented in Table 18.

Controlled Studies Answering the Focus Question 1

Out of the 10 studies (8 RCTs, 2 CCTs) that were eligible for inclusion in the qualitative analysis for focused question 1, two selected RCTs (Crespi et al., 2011b, Festa et al., 2013) and two CCTs (Serino et al 2003, Crespi et al., 2009a) were excluded from the quantitative analysis due to split-mouth or unclear design, which made pooled meta-analysis not feasible. All remaining publications had a parallel design with the patient being the unit of analysis.

The study population ranged from 15 to 58 patients. In the 6 studies included in the meta-analysis, 221 sockets were treated in a total of 214 patients. The distribution of the extracted teeth was fairly heterogeneous and included both single and multi -rooted teeth. Four studies included smokers (Barone et al., 2012, Sisti et al 2012, Barone et al., 2013a, Cardaropoli et al., 2014), while in two studies smoking habits were not reported (Iasella et al., 2003, Serino et al., 2003).

Studies Answering the Focus Question 2

Thirty studies (21 RCTs, 7 CCTs, 2 case series) were eligible for inclusion in the qualitative analysis for focused question two. From those, twelve studies compared a *GBR* approach to unassisted socket healing or to another GBR approach (Iasella et al., 2003, Cook et al., 2013, Barone et al., 2012, 2013a, 2013b, 2014, Gholami et al., 2012, Leblebicioglu et al., 2013, Patel et al., 2013, Poulias et al., 2013, Wallace et al., 2013, Cardaropoli et al., 2014). Fourteen studies compared a socket filler approach to unassisted socket healing or to different socket filler materials (Serino et al., 2003, Neiva et al., 2008, Crespi et al., 2009a, 2009 b, 2011a, 2011b, Hoang et al., 2012, Beck et al., 2010, Sisti et al., 2012, Wood et al., 2012, Festa et al., 2013, Coomes et al., 2014, Eskow et al., 2014, Spinato et al., 2014) and two studies reported implant outcomes following ridge preservation with a SS technique (Mardinger et al., 2012, Lindhe et al., 2014). Finally, two studies compared a *GBR* approach to a socket filler approach (Vance et al., 2004, Perelman-Karmon et al., 2012).

Twenty-one studies were considered for meta-analysis of at least one outcome variable following categorisation in three intervention groups: a) *GBR*: 8 RCTs (Iasella et al., 2003, Barone et al., 2012, Cook et al., 2013, Barone et al., 2013a, Patel et al., 2013, Poulias et al., 2013, Barone et al., 2014,

Cardaropoli et al., 2014) one case series (Leblebicioglu 2013) b) Socket filler: 7 RCTs (Neiva et al., 2008, Hoang et al., 2012, Sisti et al., 2012, Wood et al., 2012, Coomes et al., 2014, Eskow et al., 2014, Spinato et al., 2014) and one CCT (Beck et al 2010) c) *SS:* 1 CCT (Lindhe et al., 2014) and one case series (Mardinger et al., 2012). Two RCTs where two different types of interventions were compared (Vance et al., 2004, Perelman-Karmon et al., 2012; GBR vs. socket grafting) were categorized in both *GBR* and socket filler groups. The data from the *GBR* and the socket filler treatment groups in these two studies contributed separately to the meta-analysis of each type of intervention. Five studies were excluded from the quantitative analysis due to a split-mouth design (Crespi 2009a, 2011a, 2011b, Festa 2013, Gholami 2012) and three due to an unclear study design (Barone 2013b, Crespi 2009b, Serino 2003) which made pooled meta-analysis not feasible; one more study was excluded due to data not being provided with the patient as the unit of analysis (Wallace et al., 2013).

In the studies included in the qualitative analysis, the study population ranged from 12 to 64 patients. Following categorization into intervention groups, 280 patients were considered for the meta-analysis of *GBR* group, 242 patients for the meta-analysis of the socket filler group and 60 patients for the meta-analysis of the SS group. The distribution of the extracted teeth was heterogeneous including both single and multi-rooted teeth. Eleven studies included smokers (Barone 2012, Barone 2013, Barone 2014, Cardaropoli 2014, Cook 2013, Coomes 2014, Eskow 2014, Mardinger 2012, Patel 2013, Poulias 2013, Sisti 2012), and 5 studies non-smokers (Leblebicioglu 2013, Neiva 2008, Perelman-Karmon 2012, Spinato 2014, Wood 2012) while 5 studies did not report on smoking habits (Beck 2010, Hoang 2012, Iasella 2003, Lindhe 2014, Vance 2004).

2.6.3 Intervention characteristics

The study intervention characteristics of the included studies for both focused questions are also presented in Table 18.

Controlled Studies Answering the Focus Question 1

In 4 out of the 10 included studies (Iasella et al., 2003, Serino et al., 2003, Barone et al., 2012, Festa et al., 2013), muco-periosteal flaps were elevated both at the ARP treated and control extraction sites and in only one study in the ARP treated sites (Cardaropoli et al., 2014). It was unclear whether flaps were elevated in the ARP treated sites in one study (Crespi et al., 2011b). In the remaining 4 studies (Crespi et al., 2009a, Barone et al., 2013a, Sisti 2012, Spinato et al., 2014), a flapless approach was followed in the ARP treated sites. Primary closure was attempted however, only in one study (Barone et al., 2012). In the six included studies that specified number of intact walls, all four or at least 3 walls of the socket walls should have been intact after extraction allowing only partial loss of the buccal wall (Barone 2012, Cardaropoli 2014, Crespi 2009a, Crespi 2011b, Festa 2013, Spinato 2014). Regarding the studies

included in the meta-analysis, 2 studies required full integrity of all socket walls (Barone et al., 2012, Spinato et al., 2014), one study required minimal buccal bone loss (Cardaropoli et al., 2014) (<80%), whereas socket integrity was unclear in the remaining two studies. In 4 out of the 10 included studies, ARP was performed using a collagen barrier for GBR in combination with a porcine or bovine xenograft (Barone et al., 2012, Barone et al., 2013a, Cardaropoli et al., 2014) or an allograft (Iasella et al., 2003). In 4 studies, a collagen sheet was combined with an alloplast (Crespi 2009a, Sisti 2012), xenograft (Crespi 2011b) or allograft (Spinato et al., 2014). In one study, a porcine xenograft with a porcine cortical layer was used for grafting of the sockets (Festa 2013) and in another study, a polylactide-polyglycolide acid sponge was placed (Serino 2003).

Implant placement was attempted at 1 (Sisti 2012), 3 (Crespi et al., 2009a), 4 (Crespi et al., 2011b, Barone et al., 2013a, Cardaropoli et al., 2014, Spinato et al., 2014), 6 (Serino et al., 2003, Festa et al., 2013) or at 7 months after ARP (Barone et al., 2012). In one study, implants were placed at 4 or 6 months (Iasella 2003). In the studies where information on implant type was provided, rough surface implants were placed. Four studies did not report any information on implant type (Iasella 2003, Crespi 2009a, Festa 2013, Cardaropoli et al., 2014).

Studies Answering the Focus Question 2

In most of the studies utilising *GBR* for ARP, a muco-periosteal flap was elevated with the exception of two studies (Barone et al., 2013a, 2014-one group). On the contrary, 9 studies included a treatment group where socket filler was used (Neiva et al., 2008, Crespi et al., 2009a, 2009b, Beck et al., 2010, Crespi 2011a, Sisti et al., 2012, Coomes et al., 2014, Eskow et al., 2014, Spinato et al., 2014) and the 2 studies using *SS* techniques for ridge preservation (Mardinger 2012, Lindhe 2014) utilised a flapless approach. Very few studies besides the two studies using *SS,* attempted and/ or achieved primary closure of the soft tissues over the augmentation materials (Barone et al., 2012, 2014-one group, Gholami et al., 2012, Perelman-Karmon et al., 2012, Wallace et al., 2013). Most of the included studies for all three types of interventions, reported that all four or at least 3 walls of the socket walls should have been intact after extraction in order to proceed in ARP.

In most of the studies, GBR was performed using a collagen barrier for GBR in combination with either a porcine or bovine xenograft (Vance et al., 2004-one group, Cook et al., 2013-one group, Barone et al., 2012, 2013a, 2013b, 2014, Gholami et al., 2012- one group, Perelman-Karmon et al., 2012- one group, Patel et al., 2013- one group, Cardaropoli et al., 2014), hydroxyapatite (Cook et al., 2013-one group, Gholami et al., 2012- one group), or synthetic ceramic (Patel et al., 2013 –one group), or freeze dried bone allograft (Iasella et al., 2003, Leblebicioglu et al., 2013). An acellular dermal matrix barrier in combination with an allograft with or without the rhPDGF growth factor (Wallace et al., 2013) and

a resorbable polylactide barrier with cancellous allograft with or without bovine xenograft were used in the remaining study (Poulias et al., 2013).

Socket filling was performed using either allografts (Beck et al., 2010), xenografts (Crespi 2009b – one group, Crespi 2011a-two groups, Crespi et al., 2011b, Perelman-Karmon et al., 2012- one group, Festa et al., 2013, Neiva 2008-one group), synthetic materials (Serino et al., 2003), a combination of alloplast and collagen (Crespi 2009a, 2009b-two groups, Crespi 2011a-one group, Sisti 2012), a combination of allograft and collagen (Eskow 2014, Spinato 2014, Wood 2012), a combination of synthetic polymer, ceramic material and allograft (Vance et al., 2004-one group), a bovine-derived hydroxyapatite combined with a synthetic peptide P-15 and collagen (Neiva et al., 2008-one group), a demineralized bone matrix in bovine collagen and sodium alginate carrier (Hoang et al., 2012), or a collagen carrier with and without rhBMP-2 (Coomes et al., 2014).

The *SS* technique was performed with a porcine collagen matrix and bovine allograft (Lindhe et al., 2014) or with granulation tissue harvested from the extraction site and bovine xenograft (Mardinger et al., 2012).

Implant placement was attempted at different healing periods among all the included studies, ranging between 1.9 months (Sisti et al., 2012) to 9 months (Perelman-Karmon et al., 2012). In the GBR studies, the healing period ranged between 3-9 months, in comparison to the socket filler studies where the healing period was less than 5 months (range: 1.9 - 9 months).

In both studies that used a *SS* approach, the implants were placed at 6 months after ARP. Eleven studies did not report on the type of implants (Iasella et al., 2003, Crespi et al., 2009a, Crespi et al., 2011a, Hoang et al., 2012, Cook et al., 2013, Beck et al., 2010, Gholami et al., 2012, Wood et al., 2012, Leblebicioglu et al., 2013, Festa et al., 2013, Cardaropoli et al., 2014, Eskow et al., 2014), while in all other studies implants with a moderate rough surface were placed.

TABLE 18: *Study Characteristics of Included Papers in Systematic Review 1*

Reference	Setting (country, number, type centre)	Funding	Study design	Who carried out procedures	Number of patients (sockets)	Mean age ± SD and/or range	Smokers included	Socket location and defect morphology	Materials (details, number of patients / sockets)	Atraumatic extraction	Flap raised	Primary closure	Pre- or post-operative antibiotics	Healing period (months)	Description of implants placed	Reported follow-up after implant placement
Barone 2012[‡§]	Italy, 1 P	Unclear	RCT, Parallel	Unclear	40 (40)	26 - 69	Y	Non-molar; 4 walls	GBR (porcine bone + collagen barrier; 20/20) vs USH (20/20)	?	Y	Y	Y	7	Premium, Sweden & Martina	3 years
Barone 2013a[‡§]	Italy, 1 H	Unclear	RCT, Parallel	Specialists	58 (58)	40.5 20 - 63	Y	Molar or premolar	GBR (porcine bone + resorbable collagen barrier; 29/29) vs USH control (29/29)	?	N	N	N	4	Ossean surface, Intra-lock	None
Barone 2013b	Italy, Germany, Spain; 6, U and P?	Industry	RCT, Unclear	Unclear	38 (62)	51 ± 14	Y	Molar or premolar; excluded if facial soft tissue and buccal plate markedly reduced	GBR (bovine bone mineral (BBM) + collagen barrier; ?/31; T1) vs GBR (bovine xenograft + resorbable collagen barrier; ?/31; T2)	Y	Y	N	?	6	NanoTite Tapered Certain, Biomet 3i	None
Barone 2014[§]	Italy, 1 H	Unclear	RCT, Parallel	Specialists	64 (64)	32.7 ± 12.4 18 - 47	Y	Molar or premolar; 4 walls	GBR (corticocancellous porcine bone + resorbable collagen barrier; 32/32; T1) vs GBR (corticocancellous porcine bone + resorbable collagen barrier; 32/32; T2)	Y	T1: N T2: Y	T1: N T2: Y	Y	3	Intra-lock	None
Beck 2010[§]	USA, 1 U	Self-funded	CCT, Parallel	Unclear	33 (38)	57.4 39 - 76	?	Single root; excluded if >50% of any socket wall absent	Grafting (non–freeze-dried cancellous mineralized human bone allograft + collagen; 19/22; T1) vs grafting (non–freeze-dried cancellous mineralized human bone allograft + collagen; 14/16; T2)	Y	N	N	Y	Approx 2.5 or approx 5.5	Unclear	None
Cardaropoli 2014[‡§]	Italy, 1 P	Unclear	RCT, Parallel	Unclear	41 (48)	47.2 ± 12.9	Y	Molar or premolar; 3 intact walls and at least 80% of fourth wall intact	GBR (bovine bone mineral blended with collagen + resorbable collagen barrier; 21/24) vs unassissted healing (20/24)	Y	T1: Y C: N	N	Y	4	Unclear	None
Cook 2013[§]	USA, 1 U	Industry	RCT, Parallel	Specialist trainees	38 (40)	56 23 - 78	Y	Non-molar; excluded if bony dehiscence >50% of total socket depth	GBR (bovine bone mineral blended with collagen + resorbable collagen barrier; 20/21; T1) vs GBR (hydroxiapatite + resorbable collagen barrier; 18/19; T2)	Y	Y	N	Y	4 - 5	Unclear	1 month
Coomes 2014[§]	USA, 1 U	Industry	RCT, Parallel	Unclear	34 (34)	19 - 79	Y	Buccal bone destruction	Grafting (collagen + rhBMP-2; 18/18; T1) vs grafting (collagen; 16/16; T2)	Y	N	N	Y	5	SLA or SLActive,	None

															Institute Straumann	
Crespi 2009a	Italy, 1 H	Unclear	CCT, Split-mouth	Specialists	15 (45)	51.3 28 - 72	N	Molar or premolar; 3 bone walls and loss of buccal plate	Grafting (MHA + collagen; 15/15; T1) vs grafting (CS + collagen; 15/15; T2) vs unassisted healing (15/15)	?	N	N	Y	3	Unclear	None
Crespi 2009b	Italy, 1 U	Unclear	CCT, Unclear	Specialists	15 (45)	54.6 34 - 68	N	3 walls and loss of buccal wall	Grafting (MHA + collagen; 14/15; T1) vs grafting (CS + collagen; 14/15; T2) vs grafting (corticocancellous porcine bone + collagen; 15/15; T3)	?	N	N	Y	3	Seven, Sweden & Martina	24 months
Crespi 2011a	Italy, 1 H	Unclear	CCT, Split-mouth	Specialists	15 (45)	53.7 32 - 70	N	One molar or premolar on each side of jaw and one additional randomly located tooth to be used as a control	Grafting (MHA + collagen; 15/15; T1) vs grafting (corticocancellous xenogenic bone + collagen; 15/15; T2) vs grafting (collagen; 15/15; T3)	Y	N	N	Y	4	Unclear	None
Crespi 2011b	Italy, 1 H	Unclear	RCT, Split-mouth	Specialists	15 (30)	53.7 32 - 70	N	One molar or premolar on each side of jaw; 3 bone walls and loss of buccal plate	Grafting (corticocancellous xenogenic bone + collagen; 15/15) vs unassissted healing (15/15)	?	T1: ? C: N	T1: N C: ?	Y	4	Sweden-Martina	None
Eskow 2014[§]	USA, 1? U	Unclear	RCT, Parallel	Unclear	35 (35)	54 27 - 79	Y	Non-molar; excluded if >50% of socket wall's vertical dimension absent	Grafting (cortical FDBA + collagen; 17/17; T1) vs grafting (cancellous FDBA + collagen; 18/18; T2)	Y	N	N	Y	Approx. 4	Unclear	None
Festa 2013	Italy, 1 U	Unclear	RCT, Split-mouth	Unclear	15 (30)	28 - 58	N	Premolars: excluded if buccal or palatal/lingual bony wall fractured/lost	Grafting (corticocancellous porcine bone + soft cortical membrane; 15/15) vs unassisted healing (15/15)	Y	Y	T1: N C: Y	Y	6	Unclear	None
Gholami 2012	Iran, 1?	Unclear	RCT, Split-mouth	Unclear	12 (28)	44.6 ± 11.4 21-60	?	Non-molar; four-wall sockets	GBR (DBBM + resorbable collagen barrier; 12/14; T1) vs GBR (nanocrystalline HA embedded in silica gel matrix + resorbable collagen barrier; 12/14; T2)	Y	Y	Y	Y	6 - 8	Unclear	None
Hoang 2012[§]	USA, 1 U	Self-funded	RCT, Parallel	Unclear	30 (30)	56.1 29 - 76	?	Molar; excluded if buccal bony dehiscence >50% of length of socket	Grafting (demineralized bone matrix in a carrier of bovine collagen and sodium alginate + collagen; 16/16; T1) vs grafting (demineralized bone matrix in a carrier of bovine collagen and sodium alginate + collagen; 14/14; T2)	Y	?	N	Y	4 - 5	Unclear	None

Iasella 2003[i§]	Unclear	Unclear	RCT, Parallel	Unclear	24 (24)	51.5 28 - 76	?	Non-molar	GBR (FDBA + resorbable collagen barrier; 12/12) vs unassissted healing (12/12)	Y	Y	N	Y	4 or 6	Unclear	2 months
Leblebiciog lu 2013§	USA, 1 U	Institution al	Prospec tive case series	Specialist trainees	24 (25)	24 - 83	N	Molar or premolar	GBR (FDBA + resorbable collagen barrier; 24/25)	Y	Y	?	Y	3.7 - 8	Unclear	None
Lindhe 2014§	Unclear	Unclear	CCT, Parallel	Unclear	24 (24)	25 - 54	?	Excluded if buccal dehiscence defect ≥2 mm	Sealing (DBBM + Mucograft®; 13/13; T1) vs sealing (Mucograft®; 11/11; T2)	Y	N	Y	?	6	Astra Tech System	None
Mardinger 2012§	Israel, ?, U and P	Unclear	Prospec tive case series	Unclear	36 (43)	50.75 24 - 75	Y	Site not completely surrounded by bony walls; excluded if less than two bony wall defects	Sealing (porous bovine xenograft + intrasocket reactive soft tissue; 36/43)	Y	N	Y	Y	6	Seven MIS Implants Technologies; Tapered Screw-Vent, Zimmer Dental; Screwplant Implant Direct; Osseotite® 3i/Implant Innovations Biomet®	6 months
Neiva 2008§	USA, 1 U	Industry	RCT, Parallel	Specialists	24 (24)	25 - 76	N	Maxillary premolars with >80% bone volume in all dimensions	Grafting (anorganic bovine-derived HA matrix combined with a synthetic cellbinding peptide P-15 + collagen; 12/12; T1) vs grafting (collagen; 12/12; T2)	Y	N	N	?	3.7	Unclear	None
Patel 2013§	UK, 1 U	Industry	RCT, Parallel	Specialists	26 (26)	37.3 ± 11.4; 20 - 58	Y	Non-molar: excluded if major part of buccal or palatal wall damaged or lost	GBR (60% HA + 40% b-tricalcium phosphate + resorbable collagen barrier; 13/13; T1) vs GBR (DBBM + resorbable collagen barrier; 13/13; T2)	Y	Y	N	Y	8	Straumann standard plus SLActive implant	12 months post-loading
Perelman-Karmon 2012§	Unclear	Unclear	RCT, Parallel	Unclear	23 (23)	26 - 68	N	Non-molar; at least 50% of sockets partially resorbed/ destructed at one to two walls, but not circunferentially	GBR (bovine bone mineral + resorbable collagen barrier; 11/11; T1) vs grafting (bovine mineral bone; 12/12; T2)	?	Y	Y	N	9	Unclear	None
Poulias 2013§	USA, 1 U	Self-funded	RCT, Parallel	Specialist trainees	23 (23)	52 ± 16; 26 - 77	Y	Non-molar	GBR (cancellous allograft + resorbable polylactide barrier; 12/12; T1) vs GBR (cancellous allograft + bovine xenograft + resorbable polylactide barrier; 11/11; T2)	Y	Y	N	T1: N T2: ?	4	Unclear	None

Serino 2003	Unclear	Unclear	CCT, Unclear	Unclear	36 (39)	35 - 64	?	Unclear	Grafting (polylactide-polyglycolide acid sponge; 24/26) vs unassisted healing (12/13)	?	Y	?	N	6	Astra Tech	None
Sisti 2012[‡§]	Unclear	Unclear	RCT, Parallel	Unclear	20 (20)	50.85; 36 - 70	Y	Non-molar; buccal bone defect >5 mm	Grafting (Mg-e HA granules + collagen; 10/10) vs unassissted healing (10/10)	Y	N	N	Y	1.9	Premium, Sweden & Martina	None
Spinato 2014[‡§]	Unclear, 3 P	Self-funded	RCT, Parallel	Unclear	31 (31)	48.5; 27 - 74	N	Maxillary non-molar; four intact bony walls	Grafting (cancellous allograft + collagen; 19/19) vs unassisted healing (12/12)	Y	N	N	Y	4	Tapered Screw Vent; Zimmer Dental	None
Vance 2004[§]	Unclear	Industry	RCT, Parallel	Unclear	24 (24)	56	?	Non-molar	Grafting (carboxymethylcellulose + CS + DFDBA; 12/12; T1) vs GBR (bovine bone mineral + resorbable collagen barrier; 12/12; T2)	Y	Y	N	Y	4	Stage-1; Lifecore Biomedical	4 months
Wallace 2013	Unclear	Industry	CCT, Parallel	Unclear	30 (34)	18 - 70	N	18 intact and 16 sockets with buccal wall defects	GBR (allograft + rhPDGF-BB + acellular dermal matrix barrier; ?/19; T1) vs GBR (allograft + acellular dermal matrix barrier; ?/15; T2)	Y	Y	Y	?	4	Internal RBT Laser-Lok, BioHorizons	None
Wood 2012[§]	USA, 1 U	Industry	RCT, Parallel	Specialist trainees	33 (33)	56.7; 20 - 78	N	Single-rooted non-molar	Grafting (DFDBA + collagen; 17/17; T1) vs grafting (FDBA + collagen; 16/16; T2)	Y	?	N	Y	4 - 4.7	Unclear	None

All studies included for Question 2; highlighted studies included for Question 1

[‡] = selected for meta-analysis Question 1 [§] = selected for meta-analysis Question 2

U = university H = hospital P = private practice Y = yes N = no ? = unclear RCT = randomised clinical trial CCT = controlled clinical trial GBR = guided bone regeneration T1 = test group 1 T2 = test group 2 T3 = test group 3 C = control group

MHA = magnesium-enriched hydroxyapatite CS = calcium sulfate FDBA = freeze-dried bone allograft DBBM = deproteinized bovine bone mineral HA = hydroxyapatite DFDBA = demineralized freeze-dried bone allograft

2.6.4 Outcome characteristics

The outcomes of the included studies for both focused questions are presented in Table 19.

2.6.4.1 Studies Answering the Focused Question 1

a) Feasibility of Implant placement

All the included studies reported that implant placement was feasible in all the patients of both test (ARP) and control (unassisted socket healing) groups. For this reason, no meta-analysis was performed for this outcome variable.

b) Need for Further Augmentation

Review of the studies indicated 9 out of 10 included studies reported data on the need for further ridge augmentation, ranging between 0 - 15% for the ARP treated sites and between 0 - 100% in the unassisted socket healing sites. Six studies were included in the meta-analysis for this outcome variable (*Fig. 6a*), which appeared to be highly homogeneous (I^2= 0%, p=0.707). The pooled relative risk for further ridge augmentation was 0.150 (95% CI 0.074 to 0.302) indicating a decrease in the need for further ridge augmentation when ARP was performed.

c) Implant Survival

Eight out of 10 included studies reported data on implant survival. All implants placed in the ARP sites survived at 12 months post loading. One study (Barone et al., 2012) reported a 95% survival rate, where only one implant placed in the untreated control sites did not survive at the same observation period. Since in all of studies but one, the implant survival was 100% for both ARP and control, meta-analysis was not reported for this outcome variable.

d) Implant Success

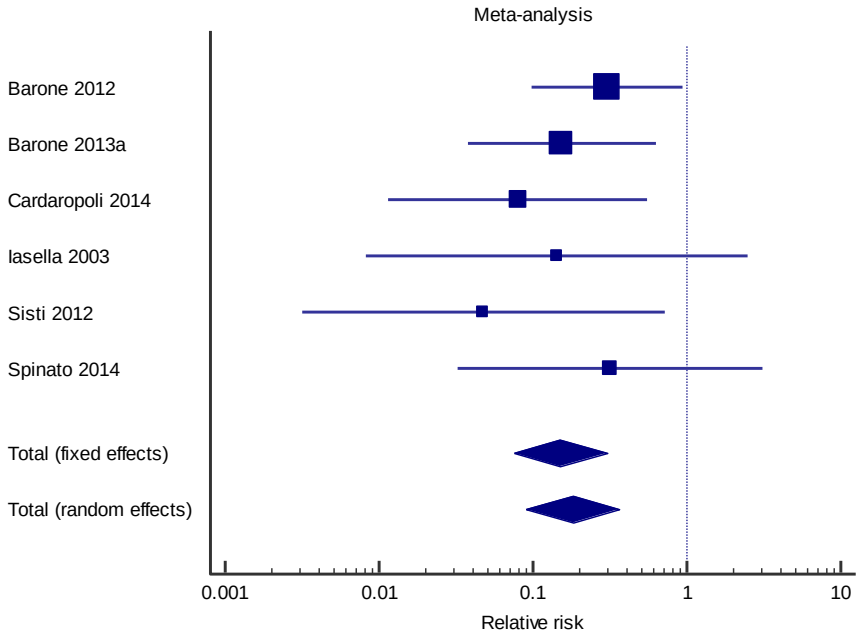
Eight out of 10 included studies reported data on implant success at 12 months post-loading. Five out of these 8 studies utilised the Albrektsson criteria (Albrektsson et al., 1985). One study evaluated success based on absence of peri-implantitis (Serino 2003), and another on the absence of proximal radiographic bone loss more than 2 mm (Spinato et al., 2014). Another study considered an implant restoration as successful when the implant was stable, without a radiolucent zone around it, no mucosal suppuration and no pain (Crespi et al., 2011b). The success rates were high for both test and control groups ranging between 95.2%-100% for the ARP treated sites and between 90% - 100% for unassisted socket healing sites. Five out of these 8 studies were included in the meta-analysis (*Fig. 6b*). The studies

were highly homogeneous (I^2= 0%, p=0.953) and the relative risk for implant failure was 1.055 (95% CI 0.945 to 1.177).

e) Marginal bone levels

Five studies reported data on proximal bone levels at 12 months post-loading (Crespi et al., 2009a, Barone et al., 2012, Sisti et al., 2012, Barone et al., 2013a, Spinato et al., 2014). One study was excluded from the meta-analysis (Crespi et al., 2009a). The studies appeared homogeneous (I^2= 0%, p=0.881). The standardised mean difference in implant proximal bone loss (mm) between ARP and non-treated extraction sites was -0.039mm (95% CI: -0.358 to 0.280) (*Fig. 6c*).

Figure 6a: *Meta-analysis for Q1 – Need for further augmentation*

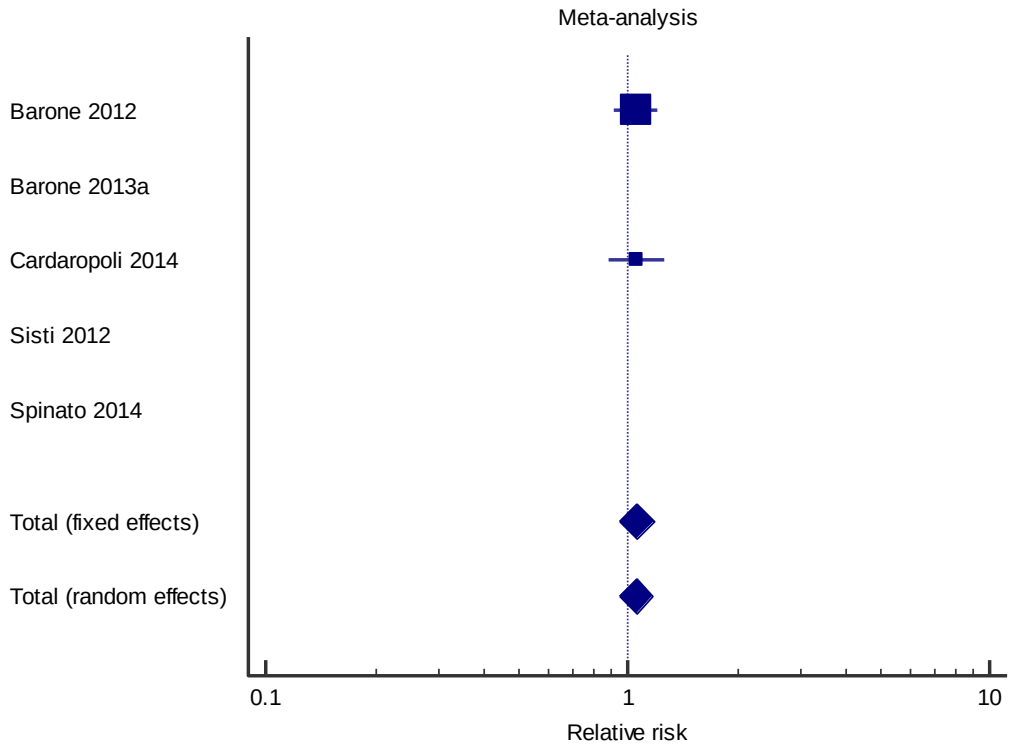


Study	Intervention	Controls	Relative risk	95% CI	z	P
Barone 2012	3/20	10/20	0.300	0.0968 to 0.930		
Barone 2013a	2/29	13/29	0.154	0.0381 to 0.622		
Cardaropoli 2014	1/21	12/20	0.0794	0.0113 to 0.556		
Iasella 2003	0/12	3/12	0.143	0.00817 to 2.499		
Sisti 2012	0/10	10/10	0.0476	0.00316 to 0.717		
Spinato 2014	1/19	2/12	0.316	0.0320 to 3.116		
Total (fixed effects)	7/111	50/103	0.150	0.0742 to 0.302	-5.304	<0.001
Total (random effects)	7/111	50/103	0.180	0.0889 to 0.365	-4.760	<0.001

Test for heterogeneity

Q	2.9535
DF	5
Significance level	P = 0.7072
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 58.28

Figure 6b: *Meta-analysis for Q1 – Success at 12 months*

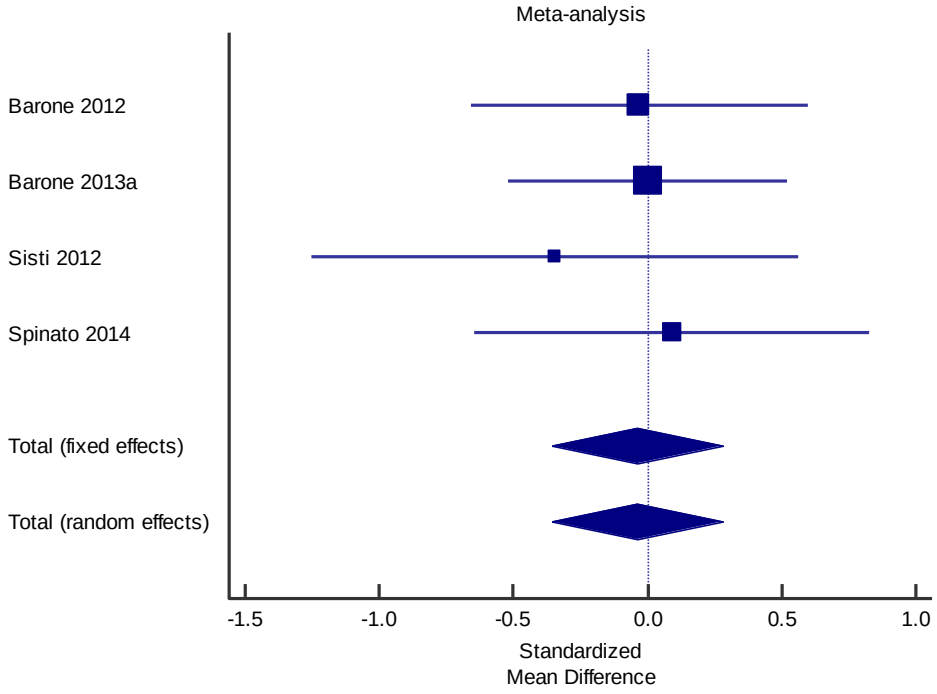


Study	Intervention	Controls	Relative risk	95% CI	z	P
Barone 2012	20/20	19/20	1.051	0.917 to 1.205		
Barone 2013a	29/29	29/29	-			
Cardaropoli 2014	20/21	18/20	1.058	0.889 to 1.260		
Sisti 2012	10/10	10/10	-			
Spinato 2014	19/19	12/12	-			
Total (fixed effects)	98/99	88/91	1.055	0.945 to 1.177	0.948	0.343
Total (random effects)	98/99	88/91	1.054	0.947 to 1.173	0.958	0.338

Test for heterogeneity

Q	0.003542
DF	1
Significance level	P = 0.9525
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 0.00

Figure 6c: Meta-analysis for Q1 – Marginal bone loss



Study	N1	N2	Total	SMD	SE	95% CI	t	P
Barone 2012	20	20	40	-0.0327	0.310	-0.660 to 0.595		
Barone 2013a	29	29	58	0.000	0.259	-0.519 to 0.519		
Sisti 2012	10	10	20	-0.348	0.432	-1.255 to 0.560		
Spinato 2014	19	12	31	0.0907	0.359	-0.644 to 0.826		
Total (fixed effects)	78	71	149	-0.0391	0.161	-0.358 to 0.280	-0.242	0.809
Total (random effects)	78	71	149	-0.0391	0.161	-0.358 to 0.280	-0.242	0.809

Test for heterogeneity

Q	0.6642
DF	3
Significance level	P = 0.8816
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 41.68

TABLE 19: *Study Outcomes of Included Papers for Systematic Review-1*

Reference	Comparison	Implant placement feasibility	Need for further augmentation	Implant survival at 12 months	Implant success at 12 months[#]	Marginal bone loss (mean ± SD or other if provided)
Barone 2012[‡§]	GBR vs unassisted healing	T 100%, C 100%	T 15%, C 50%	T 100%, C 95%	T 100%, C 95%*	T 0.75 ± 0.3, C 0.76 ± 0.3*
Barone 2013a[‡§]	GBR vs unassisted healing	T 100%, C 100%*	T 6.9%, C 44.8%*	T 100%, C 100%*	T 100%, C 100%*	T 0.9 ± 0.8, C 0.9 ± 0.7*
Barone 2013b	GBR (T1) vs GBR (T2)	T1 100% T2 100%*	T1 3.2%, T2 6.5%* (data per socket)	T1 100%, T2 96.8%* (data per socket)	T1 96.8%, T2 93.5%* (data per socket)	T1 1.2 ± 0.8, T2 1.4 ±0.9* (data per socket)
Barone 2014[§]	GBR (T1) vs GBR (T2)	T1 100%, 100%	T1 6.3%, T2 9.4%	T1 100%, T2 100%*	-	-
Beck 2010[§]	Grafting (T1) vs grafting (T2)	T1 89.5%, T2 92.9%*	-	-	-	-
Cardaropoli 2014[‡§]	GBR vs unassisted healing	T 100%, C 100%*	T 4.8%, C 60%*	T 100%, C 100%*	T 95.2%, C 90%*	-
Cook 2013[§]	GBR (T1) vs GBR (T2)	T1 100%, T2 100%	T1 10%, T2 16.7%	-	-	-
Coomes 2014[§]	Grafting (T1) vs grafting (T2)	T1 100%, T2 100%	T1 33.3%, T2 81.3%	-	-	-
Crespi 2009a	Grafting (T1) vs grafting (T2) vs unassisted healing	T1 100%, T2 100%, C 100%*	T1 0%, T2 0%, C 0%*	T1 100%, T2 100%, C 100%*	T1 100%, T2 100%, C 100%*	T1 0.18 ± 0.09, T2 0.16 ± 0.12, C 0.52 ± 0.23*
Crespi 2009b	Grafting (T1) vs grafting (T2) vs grafting (T3)	T1 100%, T2 100%, T3 100%	T1 0%, T2 0%, T3 0%*	T1 100%, T2 100%, T3 100%*	T1 100%, T2 100%, T3 100%*	T1 0.19 ± 0.09, T2 0.11 ± 0.08, T3 0.13 ± 0.10*
Crespi 2011a	Grafting (T1) vs grafting (T2) vs grafting (T3)	T1 100%, T2 100%, T3 100%	T1 0%, T2 0%, T3 0%*	T1 100%, T2 100%, T3 100%*	T1 100%, T2 100%, T3 100%*	-
Crespi 2011b	Grafting vs unassisted healing	T1 100%, C 100%*	T 0%, C 0%*	T 100% C 100%*	T 100% C 100%*	-
Eskow 2014[§]	Grafting (T1) vs grafting (T2)	T1 100%, T2 88.9%	T1 23.5%, T2 27.8%	-	-	-
Festa 2013	Grafting vs unassisted healing	T 100%, C 100%	-	-	-	
Gholami 2012	GBR (T1) vs GBR (T2)	T1 100% T2 100%	-	-	-	
Hoang 2012[§]	Grafting (T1) vs grafting (T2)	T1 100%, T2 100%	T1 6.3%, T2 14.3%	-	-	-
Iasella 2003[‡§]	GBR vs unassisted healing	T 100%, C 100%	T 0%, C 25%*	-	-	-

Leblebicioglu 2013§	GBR	100%	8.3%			
Lindhe 2014§	Sealing (T1) vs sealing (T2)	T1 100%, T2 100%*	T1 0%, T2 0%*	T1 100%, T2 100%*	-	-
Mardinger 2012§	Sealing	100%	0%	100%	-	
Neiva 2008§	Grafting (T1) vs grafting (T2)	T1 100%, T2 91.7%	T1 0%, T2 33.3%	T 100%, T2 100%*	T1 100%, T2 100%*	T1 0.32 (range 0-0.5), T2 0.79 (range 0.5-1.0)*
Patel 2013§	GBR (T1) vs GBR (T2)	T1 100%, T2 92.3%*	T1 69.2%, T2 61.5%*	T1 100%, T2 100%*	T1 84.6%, T2 83.3%*	T1 0.12 ± 0.4, T2 0.2 ± 0.58*
Perelman-Karmon 2012§	GBR (T1) vs grafting (T2)	T1 100%, T2 100%*	T1 0%, T2 0%*	T1 100%, T2 100%*	T1 100%, T2 100%*	-
Poulias 2013§	GBR (T1) vs GBR (T2)	T1 100%, T2 100%*	T1 0%, T2 0%*	-	-	-
Serino 2003	Grafting vs unassisted healing	T 100%, C 100%	T 0%, C 0%*	T 100%, C 100%*	T 100%, C 100%*	-
Sisti 2012ǂ§	Grafting vs unassisted healing	T 100%, C 100%	T 0%, C 100%	T 100%, C 100%*	T 100%, C 100%*	T 1.28 ± 0.32, C 1.45 ± 0.58*
Spinato 2014ǂ§	Grafting vs unassisted healing	T 100%, C 100%	T 5.3%, C 16.7%*	T 100%, C 100%*	T 100%, C 100%*	T 0.68 ± 0.72, C 0.61 ± 0.8*
Vance 2004§	Grafting (T1) vs GBR (T2)	T1 100%, T2 100%	T1 0%, T2 0%*	-	-	-
Wallace 2013	GBR (T1) vs GBR (T2)	T1 100%, T2 100%	T1 0%, T2 0%	-	-	-
Wood 2012§	Grafting (T1) vs grafting (T2)	T1 94.1%, T2 100%*	T1 0%, T2 0%*	-	-	-

All studies included for Question 2; highlighted studies included for Question 1

Most studies used Albrektsson et al 1986 success criteria or: Crespi 2009b - presence of implant stability, absence of a radiolucent zone around the implants, no mucosal suppuration and no pain; Serino 2003 - no Peri-Implantitis; Spinato 2014 – marginal bone loss < 2mm both mesially and distally.

ǂ = selected for meta-analysis Question 1 § = selected for meta-analysis Question 2 * = information provided by author

2.6.4.2 Studies Answering the Focus Question 2

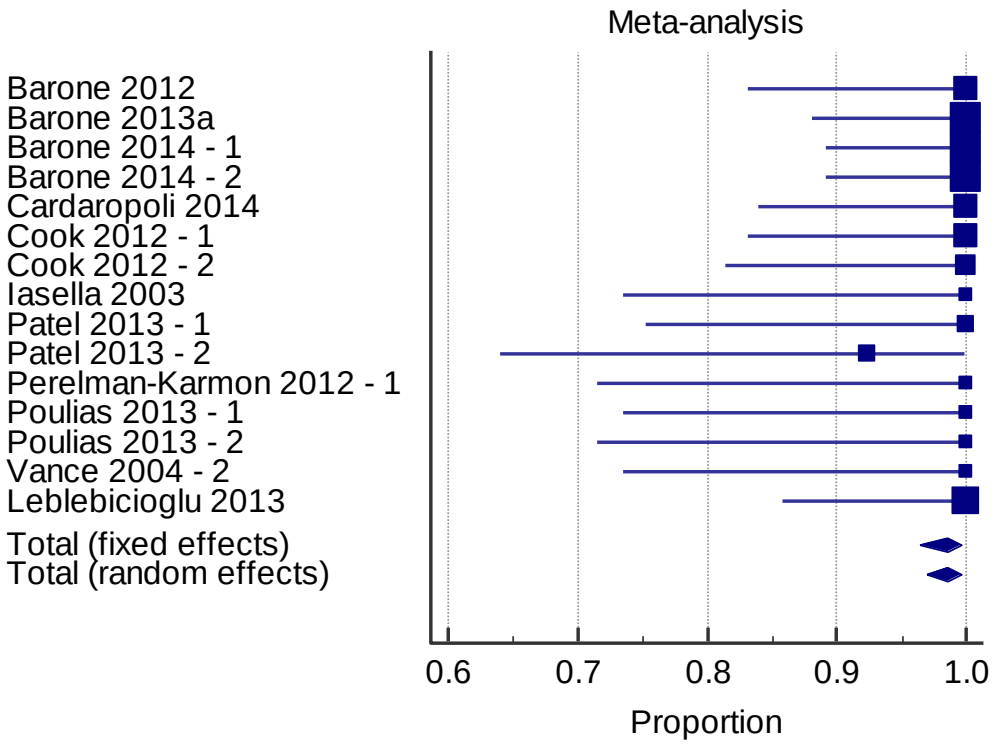
a) Feasibility of Implant Placement

Implant placement was feasible in all GBR treated sites, with the exception of one study, which reported that in one site (7.7%), implant placement was not feasible at 8 months following ridge preservation with a porcine collagen barrier and bovine bone mineral (Patel et al., 2013). Eleven studies contributed with one or two treatment groups in the meta-analysis (Iasella et al., 2003, Vance et al., 2004- one group, Barone et al., 2012, Cook et al., 2013, Barone et al., 2013a, Leblebicioglu 2013, Patel et al., 2013, Perelman-Karmon et al., 2012 – one group, Poulias et al., 2013, Barone et al., 2014, Cardaropoli et al., 2014). The studies were homogeneous (I^2= 0%, p=0.999) and the estimated pooled size effect was 98.54% (95% CI: 96.42 to 99.58) (*Fig 7a*).

Implant placement feasibility following ARP with socket filler ranged between 88.9 % and 100%. Implant placement was not feasible in 8.3% of the sockets filled with a collagen wound dressing material implant placement (Neiva et al., 2008), in 10.5% and 7.1% of the sockets filled with cancellous non- freeze dried bone allograft after 2.5 and 5 months of healing respectively (Beck et al., 2010), in 5.9% of the sockets filled with demineralised freeze dried bone allograft (Wood et al 2012) and in 11.1% of the sockets treated with cancellous freeze dried bone allograft (Eskow et al 2014). The relevant cohorts / groups from 10 studies (Vance et al., 2004- one group, Neiva et al., 2008, Beck et al 2010, Hoang et al., 2012, Perelman-Karmon et al., 2012 – one group, Sisti et al., 2012, Wood et al., 2012, Coomes et al., 2014, Eskow et al., 2014, Spinato et al., 2014) were included in the metanalysis (*Fig. 7 b*). The studies appeared homogeneous (I^2= 0%, p=0.791) and the estimated pooled size effect was 96.204% (95% CI: 93.089 to 98.182).

When a *SS* type of intervention was used (Mardinger et al., 2012, Lindhe et al., 2014), implant placement was feasible in all extraction sites treated and for this reason no meta-analysis was performed.

Figure 7a: *Meta-analysis for Q2 – Implant placement feasibility – GBR*

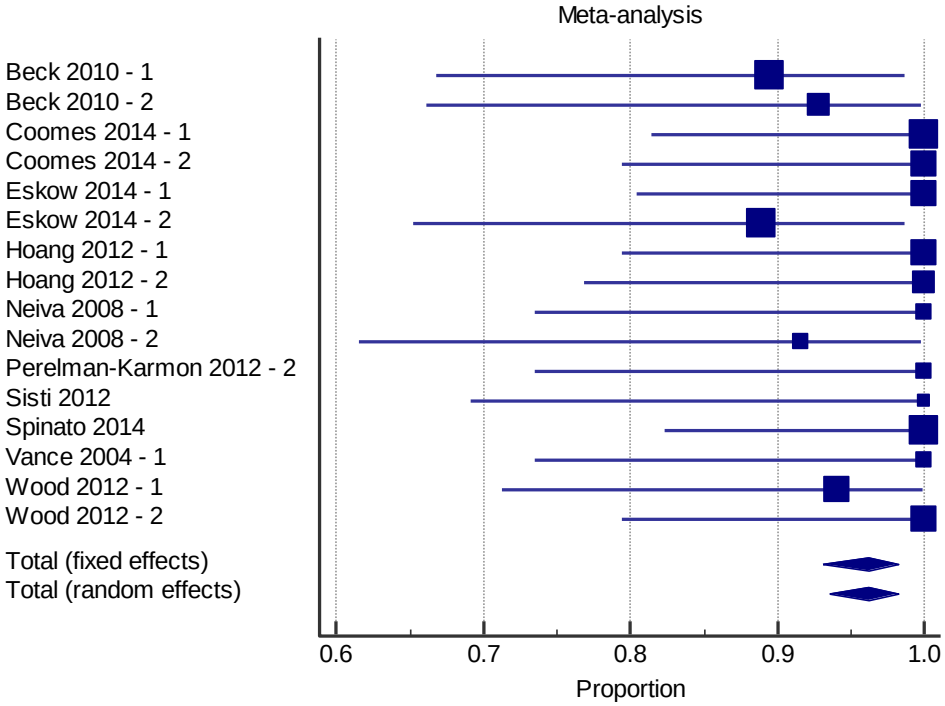


Study	Standard deviation	Proportion (%)	95% CI
Barone 2012	20	100.000	83.157 to 100.000
Barone 2013a	29	100.000	88.056 to 100.000
Barone 2014 - 1	32	100.000	89.112 to 100.000
Barone 2014 - 2	32	100.000	89.112 to 100.000
Cardaropoli 2014	21	100.000	83.890 to 100.000
Cook 2012 - 1	20	100.000	83.157 to 100.000
Cook 2012 - 2	18	100.000	81.470 to 100.000
Iasella 2003	12	100.000	73.535 to 100.000
Patel 2013 - 1	13	100.000	75.295 to 100.000
Patel 2013 - 2	13	92.308	63.970 to 99.805
Perelman-Karmon 2012 - 1	11	100.000	71.509 to 100.000
Poulias 2013 - 1	12	100.000	73.535 to 100.000
Poulias 2013 - 2	11	100.000	71.509 to 100.000
Vance 2004 - 2	12	100.000	73.535 to 100.000
Leblebicioglu 2013	24	100.000	85.753 to 100.000
Total (fixed effects)	280	98.541	96.418 to 99.576
Total (random effects)	280	98.541	96.860 to 99.591

Test for heterogeneity

Q	3.0362
DF	14
Significance level	P = 0.9990
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 0.00

Figure 7b: *Meta-analysis for Q2 – Implant placement feasibility – Grafting*



Study	Standard deviation	Proportion (%)	95% CI
Beck 2010 - 1	19	89.474	66.862 to 98.699
Beck 2010 - 2	14	92.857	66.132 to 99.819
Coomes 2014 - 1	18	100.000	81.470 to 100.000
Coomes 2014 - 2	16	100.000	79.409 to 100.000
Eskow 2014 - 1	17	100.000	80.494 to 100.000
Eskow 2014 - 2	18	88.889	65.288 to 98.625
Hoang 2012 - 1	16	100.000	79.409 to 100.000
Hoang 2012 - 2	14	100.000	76.836 to 100.000
Neiva 2008 - 1	12	100.000	73.535 to 100.000
Neiva 2008 - 2	12	91.667	61.520 to 99.789
Perelman-Karmon 2012 - 2	12	100.000	73.535 to 100.000
Sisti 2012	10	100.000	69.150 to 100.000
Spinato 2014	19	100.000	82.353 to 100.000
Vance 2004 - 1	12	100.000	73.535 to 100.000
Wood 2012 - 1	17	94.118	71.311 to 99.851
Wood 2012 - 2	16	100.000	79.409 to 100.000
Total (fixed effects)	242	96.204	93.089 to 98.182
Total (random effects)	242	96.204	93.534 to 98.187

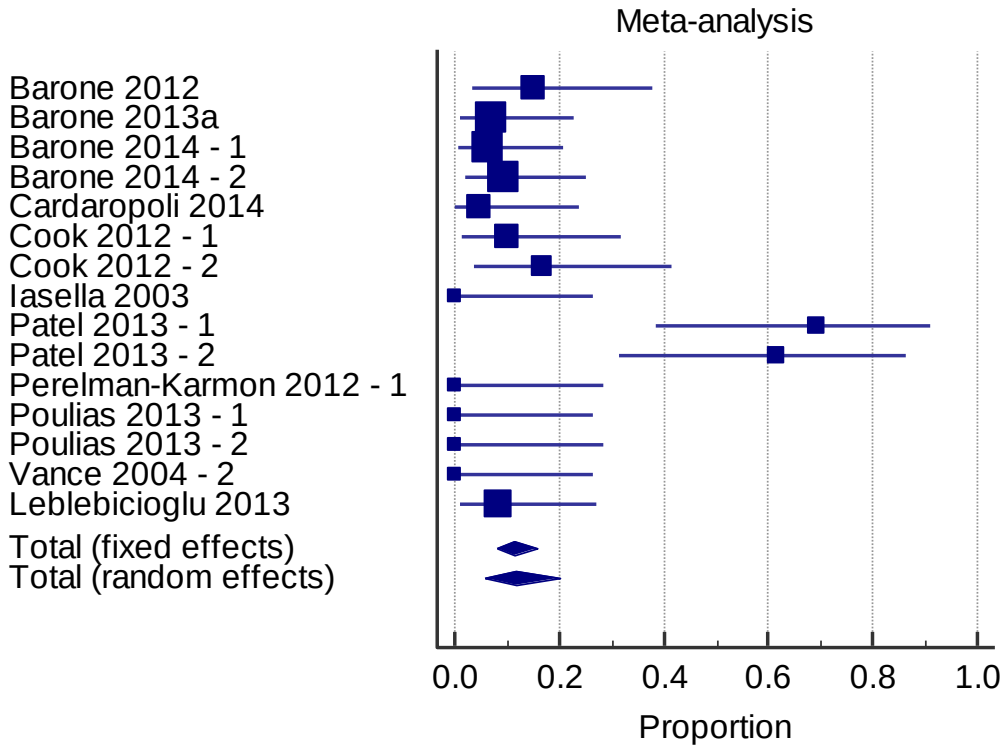
Test for heterogeneity

Q	10.4401
DF	15
Significance level	P = 0.7912
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 31.55

b) *<u>Need for Further Augmentation:</u>*

All studies in the GBR group, except one (Gholami et al., 2012), reported on the need for further ridge augmentation (range 0%-69.2%) during implant placement. Treatment groups from 11 studies were included in the meta-analysis (Iasella et al., 2003, Vance et al., 2004- one group, Barone et al., 2012, Cook et al., 2013, Barone et al., 2013a, Leblebicioglu 2013, Patel et al., 2013, Perelman-Karmon et al., 2012 – one group, Poulias et al., 2013, Barone et al., 2014, Cardaropoli et al., 2014) (*Fig. 7c*). Due to high heterogeneity among the studies (I^2= 72,97%, p<0.0001), a random effect model was used for the analysis. The estimated pooled size effect was 11.85% (95% CI: 5.642 to 19.952).

Figure 7c: *Meta-analysis for Q2 – Need for further augmentation – GBR*



Study	Standard deviation	Proportion (%)	95% CI
Barone 2012	20	15.000	3.207 to 37.893
Barone 2013a	29	6.897	0.846 to 22.766
Barone 2014 - 1	32	6.250	0.766 to 20.807
Barone 2014 - 2	32	9.375	1.977 to 25.023
Cardaropoli 2014	21	4.762	0.120 to 23.816
Cook 2012 - 1	20	10.000	1.235 to 31.698
Cook 2012 - 2	18	16.667	3.579 to 41.418
Iasella 2003	12	0.000	0.000 to 26.465
Patel 2013 - 1	13	69.231	38.574 to 90.908
Patel 2013 - 2	13	61.538	31.578 to 86.142
Perelman-Karmon 2012 - 1	11	0.000	0.000 to 28.491
Poulias 2013 - 1	12	0.000	0.000 to 26.465
Poulias 2013 - 2	11	0.000	0.000 to 28.491
Vance 2004 - 2	12	0.000	0.000 to 26.465
Leblebicioglu 2013	24	8.333	1.026 to 26.997
Total (fixed effects)	280	11.532	8.121 to 15.740
Total (random effects)	280	11.850	5.642 to 19.952

Test for heterogeneity

Q	51.7941
DF	14
Significance level	P < 0.0001
I^2 (inconsistency)	72.97%
95% CI for I^2	54.77 to 83.84

Two out of 16 included in the qualitative analysis studies that used socket filler for ARP did not report on the need for further ridge augmentation (Beck et al., 2010, Festa et al., 2013), which ranged between 0% and 81.3%. Treatment groups from 9 studies were included in the meta-analysis (Vance et al., 2004- one group, Neiva et al., 2008, Hoang et al., 2012, Perelman-Karmon et al., 2012 – one group, Sisti et al., 2012, Wood et al., 2012, Coomes et al., 2014, Eskow et al., 2014, Spinato et al., 2014) (*Fig.*

7d). Due to the high heterogeneity among the studies (I^2= 81.22%, p<0.0001), a random effect model was used for this analysis. The estimated pooled size effect was 13.65% (95% CI: 5.042 to 25.588).

Finally, no further augmentation was necessary in any extraction site when a SS type of intervention was used.

c) Implant Survival

The qualitative analysis included 7 out of 14 studies that used GBR and 9 out of the 16 studies that used socket filler together with the 2 studies that used SS reporting data on implant survival. In all studies, the implant survival for the ARP treated sites was 100%; therefore, meta-analysis was not performed for this outcome variable.

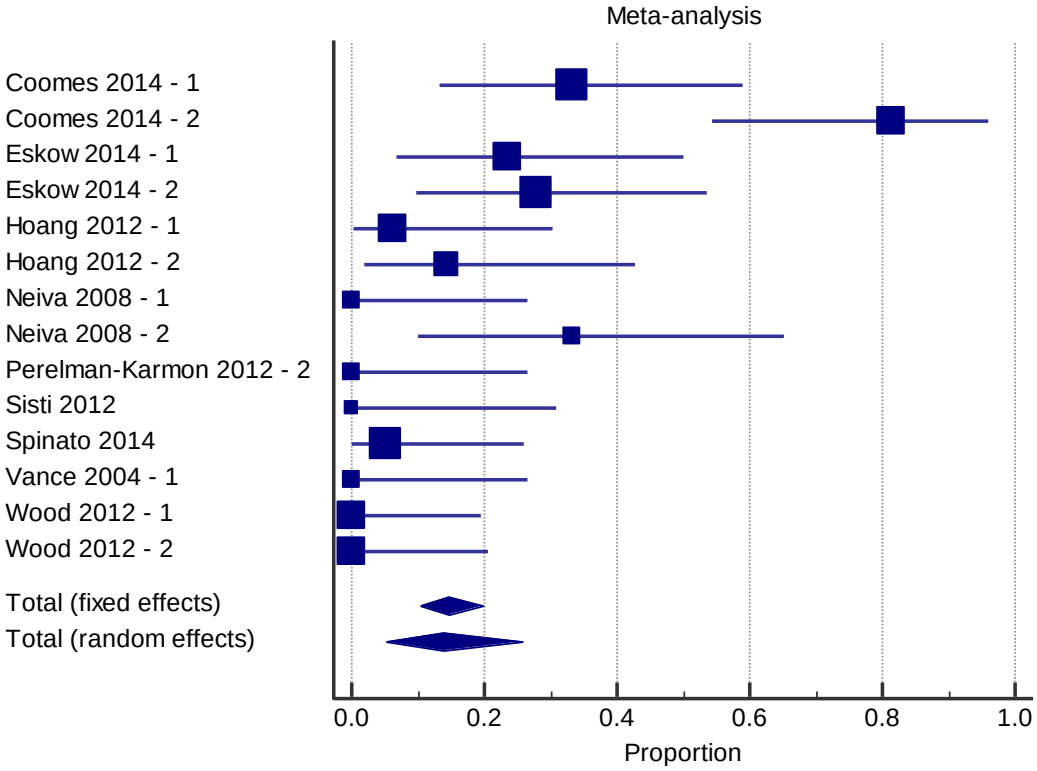
d) Implant Success

The qualitative analysis included 6 out of 14 of the included studies. These studies undertook GBR and reported on implant success at 12 month post-loading, based on the Albrektsson criteria. The success rates in the different GBR treatment groups, ranged between 83.3 and 100%. Five studies contributed one or two treatment groups to the meta- analysis (Barone et al., 2012, 2013a, Perelman-Karmon et al., 2012, Patel et al., 2013, Cardaropoli et al., 2014) (*Fig 7.e*). The studies were not homogeneous (I^2= 54.77%, p=0.0503) and the random effect model showed an estimated pooled size effect for implant success of 93.976% (95% CI 85.708 to 98.833).

Nine out of 16 studies used a socket filler and were included in the qualitative analysis studies. These studies reported on implant success at 12 month post loading (Serino et al., 2003, Neiva et al., 2008, Crespi et al., 2009a, 2009b, 2011a, 2011b, Perelman-Karmon et al., 2012- one group, Sisti et al., 2012, Spinato et al., 2014). Six studies evaluated implant success based on Albrektsson criteria and the remaining three on either presence of implant stability, absence of a radiolucent zone around the implants, no mucosal suppuration and no pain (Crespi 2009b) or absence of peri-implantitis (Serino 2003) or radiographic proximal bone levels (Spinato 201). All of these studies reported success rates of 100% therefore no meta-analysis was performed.

None of the two studies utilising a SS approach reported on implant success at 12 months post loading.

Figure 7d: *Meta-analysis for Q2 – Need for further augmentation – Grafting*

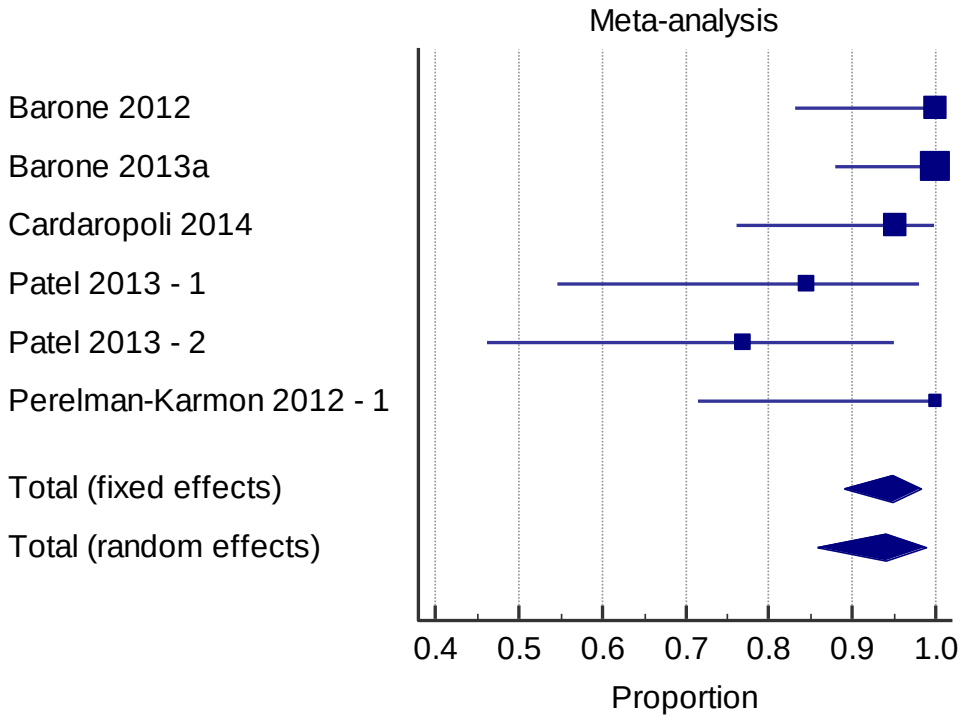


Study	Standard deviation	Proportion (%)	95% CI
Coomes 2014 - 1	18	33.333	13.343 to 59.007
Coomes 2014 - 2	16	81.250	54.354 to 95.953
Eskow 2014 - 1	17	23.529	6.811 to 49.899
Eskow 2014 - 2	18	27.778	9.695 to 53.480
Hoang 2012 - 1	16	6.250	0.158 to 30.232
Hoang 2012 - 2	14	14.286	1.779 to 42.813
Neiva 2008 - 1	12	0.000	0.000 to 26.465
Neiva 2008 - 2	12	33.333	9.925 to 65.112
Perelman-Karmon 2012 - 2	12	0.000	0.000 to 26.465
Sisti 2012	10	0.000	0.000 to 30.850
Spinato 2014	19	5.263	0.133 to 26.028
Vance 2004 - 1	12	0.000	0.000 to 26.465
Wood 2012 - 1	17	0.000	0.000 to 19.506
Wood 2012 - 2	16	0.000	0.000 to 20.591
Total (fixed effects)	209	14.511	10.165 to 19.830
Total (random effects)	209	13.649	5.042 to 25.588

Test for heterogeneity

Q	69.2137
DF	13
Significance level	P < 0.0001
I^2 (inconsistency)	81.22%
95% CI for I^2	69.51 to 88.43

Figure 7e: *Meta-analysis for Q2 – Success at 12 months*



Study	Standard deviation	Proportion (%)	95% CI
Barone 2012	20	100.000	83.157 to 100.000
Barone 2013a	29	100.000	88.056 to 100.000
Cardaropoli 2014	21	95.238	76.184 to 99.880
Patel 2013 - 1	13	84.615	54.553 to 98.079
Patel 2013 - 2	13	76.923	46.187 to 94.962
Perelman-Karmon 2012 - 1	11	100.000	71.509 to 100.000
Total (fixed effects)	107	94.818	88.968 to 98.104
Total (random effects)	107	93.976	85.708 to 98.833

Test for heterogeneity

Q	11.0542
DF	5
Significance level	P = 0.0503
I^2 (inconsistency)	54.77%
95% CI for I^2	0.00 to 81.86

e) Marginal Bone Levels

Data on radiographic proximal bone levels at 12 months post-loading was reported in 4 studies where GBR has been used for ARP (Barone et al., 2012, 2013a, 2013b, Patel et al., 2013). The average radiographic bone loss in implants proximal sites ranged among these studies between 0.12 ± 0.4mm to 1.4 ± 0.9 mm. One study was excluded from meta-analysis (Barone 2013b) because of unclear study design and the patient was not used as the unit of analysis. Since only 3 studies were finally included in the metanalysis, the results are not presented.

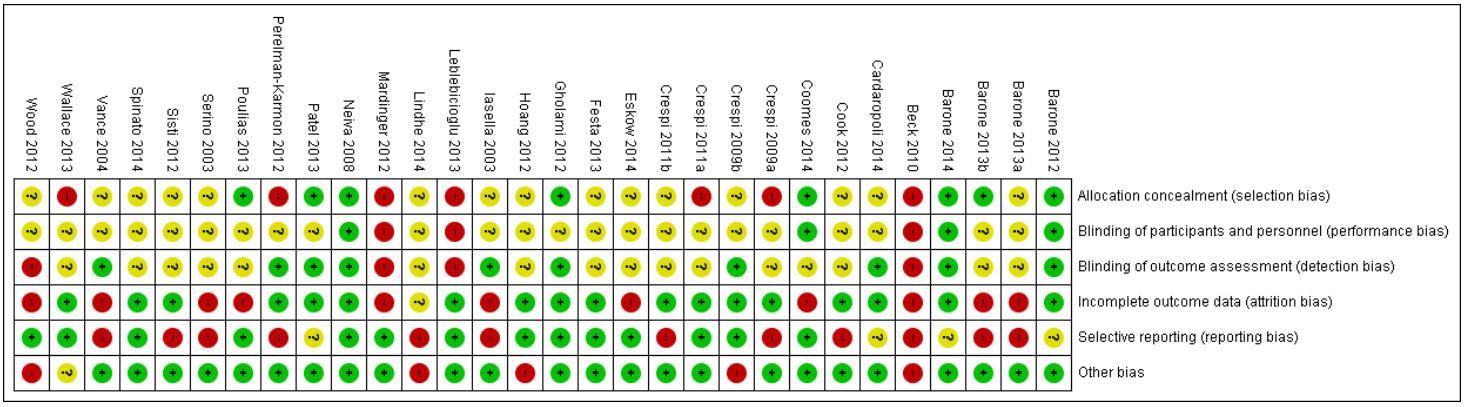
Five out of 16 studies included in the qualitative analysis that used socket filler reported on radiographic proximal bone levels at 12 month post loading (Neiva et al., 2008, Crespi et al., 2009a, 2009b, Sisti et al., 2012, Spinato et al., 2014). Average radiographic bone loss ranged between 0.11 ± 0.08 mm to 1.28

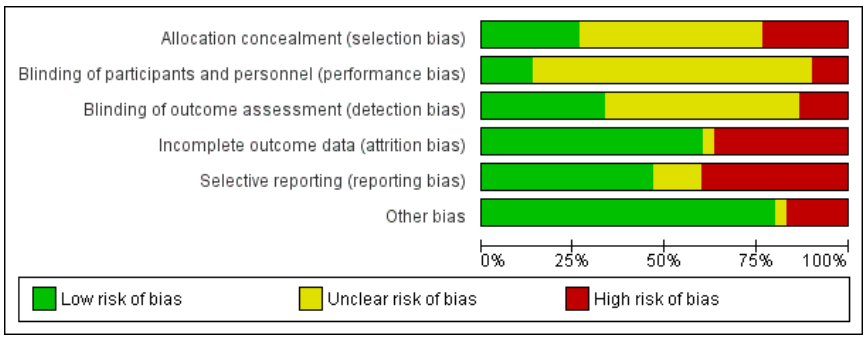
± 0.32 mm. A meta-analysis was not performed for this type of intervention since 2 studies were excluded because of split-mouth design (Crespi et al., 2009a, 2009b) and one study because no standard deviation/ standard error of the mean was reported (Neiva et al, 2008). None of the two studies utilising a SS approach, reported on radiographic proximal bone levels.

2.6.5 Quality assessment and risk of bias

The quality assessment of all the included studies for both focused questions are presented in figures *8a* and *8b*. There was only one study (Neiva et al., 2008) complying with all the criteria for bias and it was considered to have a low risk of bias. Three studies presented low risk of bias in 5 out of the 6 domains and unclear risk in one domain (Barone et al., 2012, Barone 2014, Gholami et al., 2012), one study presented low risk in 4 domains and unclear in 2 (Patel 2013) and three studies presented low risk of bias in 3 domains and unclear risk in the other three (Festa et al., 2013, Cardaropoli et al., 2014, Spinato et al., 2014). All these studies were considered to have an unclear risk of bias. All other studies were considered to be at high risk of bias. Reporting and attrition were the most common sources of bias while selection, performance and other sources of bias were of less concern in most of the studies. (*Fig 8a and 8b*). In several studies however, allocation concealment, blinding of participants and personnel or outcome assessment was not clearly reported resulting in unclear risk of bias for these domains.

Figures 8 a, b: *Quality assessment of the included papers: (Above) Risk of bias graph. (Below) Risk of bias summary*





2.7 Discussion

2.7.1 Objective and main findings

Recent systematic reviews and meta-analyses have demonstrated that although post-extraction resorption of the alveolar ridge cannot be totally prevented, various ARP procedures will reduce vertical and horizontal hard and soft tissue dimensional changes and will support new bone formation in the extraction socket (Horváth et al., 2012, Vignolleti et al., 2012, Wang and Lang 2012, De Risi et al., 2013, Morjaria et al., 2014, Avila-Ortiz et al., 2014). However, the same systematic reviews emphasized the fact that there is limited evidence on the influence of ARP on implant related outcomes. Considering that these procedures are performed mostly to facilitate implant placement in the post extraction sites, such information could be of high clinical relevance since clinicians may argue against the extensive use of ARP procedures, if implant placement feasibility and need for ridge augmentation is not significantly decreased, when compared to unassisted socket healing (Horváth et al., 2012, Vignolleti et al., 2012, Wang and Lang 2012, De Risi et al., 2013, Morjaria et al., 2014, Avila-Ortiz et al., 2014). The present systematic review evaluated the evidence derived from existing RCTs, CCTs and large prospective case series, that reported on implant related outcomes following different ARP surgical protocols. The outcome variables selected were implant placement feasibility, need for further ridge augmentation during implant placement, implant survival/success rates and proximal bone levels of the implants placed in the preserved alveolar ridges at least 12 months after implant loading. The meta-analyses result from both focused questions, demonstrated that dental implants could be placed in the vast majority of the patients that were treated with ARP and that all implants survived and experienced high success rates, without significant proximal bone loss. Proximal bone loss did not appear to be dependent on the type of intervention used in the ARP technique. These findings are in agreement with previous systematic reviews, which assessed qualitative implant related outcomes (Horváth et al., 2012, Vignolleti et al., 2012).

2.7.2 Strengths and Weakness of the Systematic Review

In comparison to previous systematic reviews, the present study has exclusively evaluated implant related outcomes following ARP. The review has attempted to answer two different focused questions. For the first focused question, the search and analysis was limited to RCTs, CCTs and prospective cohort studies, with a control group of unassisted socket healing. The review was based on the statement that the clinical merit of applying ARP, was on the understanding that ARP techniques facilitate implant treatment, improved implant placement feasibility, reduced the need for further ridge augmentation and improved implant survival, success and marginal bone levels, when compared to unassisted socket healing. For the second focused question, controlled studies included groups other than unassisted

socket healing and contained large prospective case series in the search, in order to utilise as much of the available research data as possible. The studies were categorised according to the type of ARP intervention, in order to provide average incidences for each of the previously described implant related outcomes.

Although a comprehensive search strategy was adopted, which included 5 databases, extensive hand and cross-reference search, with no language restrictions applied, it is possible that some grey literature may not have been included, particularly as only published studies were selected. To obtain as much data as possible from the published studies, the authors of 34 out of 103 of the fully screened studies were conducted by e-mails and asked to provide further information and clarification on outcome measures, especially in relation to implant outcomes. A large part of the provided information utilised in the analyses of both focused questions, was provided directly by the authors and is not published in the original papers. On the other hand, some authors failed to respond within the requested period of time; therefore, it is possible that the available data was more comprehensive than that reported.

The total number of included subjects and selected studies identified for *Focused Question 1* was considered sufficient for the assessment of the effect size differences between ARP and unassisted socket healing, when reviewing implant related outcomes such as further ridge augmentation and implant placement feasibility. Similarly, the total number of patients and studies included in the meta-analysis for *Focused Question 2* could be considered sufficient for the assessment of average incidences of the need for additional augmentation, when GBR or socket fillers were used for ARP. However, limited data was available to evaluate the influence of SS techniques on implant related outcomes. Furthermore, the metanalysis results for some treatment outcomes (e.g., success rates and marginal bone loss) should be evaluated with caution, given the limited number of studies reporting on these outcomes that were eligible for inclusion in the quantitative analysis.

Finally, the sample sizes of the selected trials were relatively small and only few trials included a sample size calculation; this may have reduced the power of the studies.

Focused Question 1

Qualitative and quantitative analysis of the included studies for *Focused Question 1,* demonstrated that the application of ARP procedures would significantly decrease the need for additional ridge augmentation during implant placement, when compared to unassisted socket healing. This observation was in agreement with the qualitative analysis undertaken by Horváth et al. (2012) and the observations from other studies that were not included in the analysis (Fiorellini et al., 2005, Pellegrini et al., 2014). The requirement for additional augmentation was the only outcome variable, where statistically significant differences were detected between ARP and unassisted socket healing. Interestingly enough, all the included studies reported that implant placement was feasible in all the patients of both

test (ARP) and control (unassisted socket healing) groups. These results are in agreement with Serino et al., 2008 (excluded from the current analysis) who reported that implants could be placed in all patients, independently of whether ARP was undertaken. It could be argued however, that several surgical factors such as the anatomic location, the angulation of implant placement according to a prosthetically driven implant placement protocol or the diameter of the used implants may have influenced both the implant placement feasibility and the need for further ridge augmentation (Mardas et al., 2010).

In the present study, there was no clear evidence that ARP procedures increased implant placement feasibility, improved the survival or success of the implants placed in post extraction alveolar ridges or contributed to the maintenance of marginal proximal bone levels, when compared against unassisted socket healing. Histological healing of the socket should be also considered when implant placement is scheduled after extraction with or without ARP (Hämmerle et al., 2012). It is possible that besides a reduction in post-extraction dimensional changes, ARP does not promote or accelerate new bone formation, when compared to unassisted socket healing, or is able to guide the histological events or limited physiologic resorption of the bundle bone. (Hämmerle et al., 2012, De Risi et al 2013).

Focused Question 2

Although various surgical techniques and materials have been used for ARP, no material or type of ARP intervention can be claimed to yield superior results to another (Horváth et al., 2012). Previous systematic reviews concluded that the use of barriers for GBR appeared to be more effective in limiting post extraction dimensional changes of the alveolar ridge (Horváth et al., 2012, Vignolleti et al., 2012, Avila-Ortiz et al., 2014). In the present systematic review, we evaluated implant related outcomes following ARP with three different types of interventions: GBR, socket filler and SS. Although, direct statistical comparison was not possible, the reported average incidences for implant placement feasibility, or the need for additional augmentation between subjects treated with one intervention or another was similar. In the vast majority of the subjects, implants were successfully placed and restored, whilst all implants survived at 12 months after loading, independently of the intervention used for ARP. However, the need for further augmentation varied significantly within the different studies and type of interventions, ranging from 0% to 81.3%. This variation may indicate that several factors besides the type of intervention may have contributed to the clinical decision to perform further grafting during implant placement. Besides the different materials and type of interventions, we could speculate that differences in implant size and design, the surgical protocol; implant angulation and the anatomic location may have contributed to the great variance observed. The high level of heterogeneity between the studies included in each intervention type may also reflect these differences.

2.7.3 Risk of bias, quality assessment and confounding factors

The quality of the included studies for both focused questions has been assessed in this review to estimate the source and magnitude of potential bias that may lead to inaccurate conclusions. Based on the quality assessment, the results presented should be evaluated with caution since only one study included in the qualitative and quantitative analysis for *Focus Question 2* presented with a low risk of bias (Neiva et al., 2008), while none of the trials included in the qualitative and quantitative analysis for *Focus Question 1* have qualified as low risk of bias. Six out of the 10 studies included in the analysis for *Question 1* and 22 out of the 30 studies for *Question 2* were qualified for a high risk of bias. These studies presented with high risk of bias in at least 2 domains. Similar concerns about the quality of the currently available studies on the effect of different ARP procedures have been raised in other systematic reviews (Horváth et al., 2013, Vignoletti et al., 2012, Morjaria et al., 2014). Inadequate or selective reporting and incomplete data outcomes were the most common sources of bias in our study.

The lack of universally accepted success and survival criteria for implant-supported restorations is a significant obstacle in comparing the different studies and surgical protocols in implant dentistry (Donos et al., 2008). The fact that different success criteria were used in the included studies, and progressive marginal bone loss around the implants was evaluated over a short term, using in most cases non-standardised x-rays, creates difficulties in the interpretation of the results for these treatment outcomes.

A plethora of confounding factors may also have influenced implant related outcomes, following the ARP procedures. These ARP studies have included different biomaterials, surgical techniques and protocols, which have been combined in the qualitative and quantitative analyses for both focused questions. There may also be specific clinical reasons why different ARP procedures have been applied after extraction of different types of teeth, representative of individual patient variation and possibly smoking habits. Differences were also reported in the anatomical, dimensional characteristics, gingival tissue biotypes and implants sizes placed at various healing periods after ARP. This lack of consistency and standardisation may have contributed to the high heterogeneity observed especially in relation to the need for further augmentation when extraction sites were treated with GBR or socket fillers and should be taken under consideration, in the interpretation of the results of both metanalyses.

Previous systematic reviews suggested a possible beneficial effect of flap elevation (Vignolleti et al., 2012, Avila-Ortiz et al., 2014), use of membrane (Horváth et al., 2012, Vignolleti et al., 2012, Avila-Ortiz et al., 2014) and the use of xenograft or allograft (Avila-Ortiz et al., 2014) on the preservation of pre-extraction ridge dimensions. In the present study, it was not possible to apply any subgroup analyses exploring potential differences in treatment effect between flap and flapless protocols, different bone grafts/fillers or different healing periods; therefore, we were not able to estimate the effect of these confounders on implant treatment outcomes. On the other hand, this systematic review found comparable implant related outcomes following ARP with GBR and socket fillers, failing to identify a

beneficial effect of using a barrier membrane on any of the investigated implant related outcomes. Furthermore, the present qualitative analysis showed that the use of allografts for socket grafting in 3 studies (Beck et al., 2010, Wood et al 2012 Eskow et al 2014) resulted in decreased implant placement feasibility in comparison with other grafting/filler materials. This finding is in contradiction with the systematic review by De Risi et al (2013) who reported higher values of bone formation following ARP with allografts in comparison to xenografts. Differences in the clinical management of these materials and in implant placement protocol, as well as the fact that different studies were included in the two systematic reviews should be considered as the reason for these discrepancies. Currently, there is no evidence correlating histological healing and implant related outcomes and it is not known which type of grafting material could serve superior to another in terms of histological healing and implant related outcomes.

The timing of implant placement following ARP varied significantly between the included studies for both focused questions (Table 18). It might be argued that longer healing periods could have improved implant related outcomes allowing more time for the mineralization of bone tissue in the socket. However, this was not obvious in the present systematic review where comparable survival and success rates were achieved between studies placing implants at different healing periods after ARP. Similar suggestions have been made in another systematic review evaluating histological outcomes following ARP where the authors suggested that implant placement could be performed after 3 or 4 months of healing independently of the grafting materials used (De Risi et al., 2013).

2.8 Conclusion

Within the limitations of present study, the following conclusions can be drawn. Alveolar ridge preservation procedures may decrease the need for further ridge augmentation during implant placement, in comparison to unassisted socket healing, potentially simplifying the surgical treatment during implant fixture placement. The systematic review did not find evidence to support the fact that implant placement feasibility was increased following ARP, in comparison to unassisted socket healing, with the survival, success and marginal bone levels of implants placed in alveolar ridges following ARP, comparable to that of implants placed in untreated sockets.

No evidence was identified to inform on the possible superior impact of a type of ARP intervention (GBR, socket filler and SS*)* on implant outcomes, with current evidence unable to demonstrate whether a specific biomaterial or treatment protocol is superior to others.

The majority of the studies evaluating implant related outcomes after ARP procedures are presenting high or unclear risk of bias; therefore, any clinical recommendation derived from these studies should be applied with caution.

Chapter 3

Hard And Soft Tissue Changes Following Alveolar Ridge Preservation: A Systematic Review

3.1 Introduction and study aims

Alveolar bone and soft tissue remodelling are a normal physiological response following tooth extraction. The bone resorption process has been recorded as leading to a 40-60% decrease in the height and the width of the residual alveolar ridge (Johnson, 1969, Farmer and Darby, 2014)) resulting in narrowing of the keratinized mucosa and a reduction in the soft tissue thickness (Thoma et al., 2009, Tarnow et al., 1996, Jemt, 1997, Schropp et al., 2003b, Darby et al., 2009). The resorption process varies greatly amongst individual patients and tooth position and may be affected by several factors such as the presence of infection, previous periodontal disease, the extent of a traumatic injury and the number or the thickness of the bony socket walls (Garg and Guez, 2011). An equilibrium is reached approximately 3-4 months post-extraction, resulting in a bone and soft tissue level that is lower than that of the neighbouring teeth, as complete regeneration of the socket site never occurs (Amler, 1969).

Although bone substitutes were able to maintain the tissue contours in extraction sites, the conservancy of the gingival and bone tissue has been found to be variable. Marked differences in the quantity and the quality of the regenerated tissue have been reported, with the presence of the graft sometimes identified as interfering with the normal healing process (Froum et al., 2002b, Mardas et al., 2010, Horváth et al., 2013, Hsun-Liang et al., 2013).

Although there is recognition that various ARP techniques can be used to preserve and promote alveolar bone and soft tissue development in the extraction socket area (Vignoletti et al., 2012, Wang and Lang, 2012, Avila-Ortiz et al., 2019) heterogeneity of the published data has led Vignoletti et al. (2012) and Horváth et al. (2013) to conclude that the clinical outcome and prosthetic options available following ARP are inconclusive.

This systematic review and meta-analysis have been designed to investigate the effects of alveolar ridge preservation on bone and gingival tissue site dimensions, keratinised tissue width, histological bone characteristics and patient-based outcomes. Furthermore, it was designed as an extension and update of the systematic reviews undertaken by Horváth et al. (2013) and was based on the methodological structure of the first systematic review outlined in this thesis.

12.2 Study protocol

The investigative design and study protocol was designed according to the Cochrane and EAO requirements for a consensus report. The study population, inclusion and exclusion criteria, search strategy and assessment of bias, are consistent with the first systematic review and will not be repeated in the description of this second systematic review methodology.

This new investigation aimed to examine the therapeutic concepts for improving dental implant outcomes following tooth extraction. Two focused questions were asked:

Focused Question 1:

The main focused question of this systematic review was:

"**Are there any additional benefit of alveolar ridge preservation techniques over unassisted healing in terms of the following: (i) horizontal and vertical alveolar ridge dimensions, (ii) soft tissue conservancy measured through linear and volumetric analysis (iii) histological characteristics of the bone, (iv) keratinised tissue dimensions (V) and patient-based outcomes?"**

Focused question 2:

In order to examine data published in case series and in controlled clinical studies, where unassisted socket healing has not been used as a control group, but different ARP procedures were compared or data published in case series, this systematic review attempted to address a second focused question:

"What are the estimated size effects on (i) horizontal and vertical alveolar ridge dimensions, (ii) gingival tissue conservancy measured through linear and volumetric dimensional changes, (iii) histological characteristics of the bone, (iv) keratinised tissue dimensions (V) and patient-based outcomes, following different alveolar ridge preservation techniques?"

3.2.1 Types of studies examined

For **Focused Question 1**, only longitudinal prospective studies, i.e., RCTs and CCTs with unassisted socket healing as a control group, were included in the meta-analysis.

For **Focused Question 2**, in addition to the previous studies, RCTs, CCTs and large prospective case series without an unassisted healing control group, were included in the meta-analysis.

3.3 Methodology

3.3.1 Study population

Healthy individuals, without any age limit, who underwent any type of ARP following permanent tooth extraction. Studies including smokers and patients with a history of periodontal disease were not excluded.

Specific Inclusion Criteria for Focused Question 1

The study inclusion criteria included:

a. Longitudinal prospective studies, i.e., RCTs and CCTs where one of the above-mentioned types of interventions was carried out in the test group and where unassisted socket healing was used as a control group.

b. Studies reporting on a minimum of 10 patients per group

c. Follow-up time longer than 3 months.

Specific Inclusion Criteria for Focused Question 2

The study inclusion criteria included:

a. Longitudinal prospective studies, i.e., RCTs, CCTs, cohort studies where one or more of the above-mentioned types of interventions was carried out, with or without unassisted socket healing as a control group and prospective case series.

b. Controlled studies reporting on a minimum of 10 patients per group, or case series reporting on a minimum of 20 patients.

c. Follow-up time longer than 3 months.

3.3.2 Types of Intervention

Examined studies reported on the following test and control groups:

Test Groups

Studies reporting on any of the following ARP interventions were included:

a) Socket grafting with autographs, allografts, xenografts, alloplast and substitutes with biologically active materials (growth factors)

b) GBR with various barrier membranes and combinations of the above grafting materials.

c) SS procedures using a combination of soft tissue graft and the above grafting materials.

Control Groups

The control group for **Focused Question 1 and 2** was unassisted socket healing, following atraumatic tooth extraction with unassisted healing.

3.3.3. Outcome Variables

For both focused questions, the following outcome variables were evaluated:

a) **Linear and/ or area changes:** in vertical alveolar bone height.
b) **Linear and/ or area changes:** in alveolar bone width.
c) **Soft tissue dimensional changes**: expressed as a change in tissue thickness (mm).
d) **Histological characteristics:** Expressed as a percentage of new bone, residual graft matrix and connective tissue formation.
e) **keratinised tissue:** expressed as a change in the width and thickness (mm) of the attached mucosa.
f) **Post-operative complications** and **patient-based outcomes**.

3.4 Research synthesis and meta-analysis

For all included studies answering both focused questions, a descriptive synthesis was undertaken. The studies were classified according to research design and type of intervention and the outcomes were recorded in evidence tables.

For **Focused Question 1**, meta-analysis was conducted utilising the available data from the selected RCTs and CCTs studies. The analysis was undertaken separating the studies according to parallel and split mouth designs and was only carried out if each group contained more than 2 eligible studies.

For **Focused Question 2**, meta-analysis was conducted utilising the available data from all the studies included in the analysis of focused question 1 and data from RCTs and CCTs with parallel design, as well as larger prospective case series. The studies included for meta-analysis were divided into three different groups (*GBR, socket grafting and SS*) according to the type of intervention, and analysis was only carried out if each group contained more than 2 eligible studies. When ARP was performed utilising a resorbable or non-resorbable barrier membrane, the study was categorised in the *GBR* group. This was independent of whether an additional bone grafting material was used. When the socket was treated with a bone or substitute graft, including collagen sponges / plaques and growth factors, the study was categorised in the *socket grafting* group. Finally, the study was categorised in the *SS* group

when a soft tissue graft was used to seal the entrance of the socket with or without grafting of the socket following a flapless approach.

MedCalc® Version 15.11.0 (MedCalc Software bvba, Ostend, Belgium) software was used for the meta-analyses for focused question 1. For Question 2, Comprehensive Meta-Analysis Version 3.3.070 (Biostat, Inc., Englewood, USA) software was used. When several intervention groups were reported on, these were combined into one single intervention group, as advised in The Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green 2011).

Assessment of statistical heterogeneity was performed using Cochran's Q-test and determination of the I^2 index (Higgins et al., 2003). The I^2 index provides an estimate of the amount of variation attributable to heterogeneity (I^2 = 25%: low; I^2= 50%: moderate; I^2= 75%: high heterogeneity). The different outcome variable estimates were pooled using a random effects model, as the effect of ARP was anticipated as varying between individual studies (Borenstein et al.,2009).

For **Focused Question 1 and 2**, a standardised mean difference (i.e., the difference in means divided by the standard deviation) was calculated for continuous variables. For **Focused Question 2**, Forest Plots were created to illustrate the effects of the different studies, shown against the global estimate. Statistical significance was achieved if $p < 0.05$. The unit of analysis used for the study was the patient. Results are given as mean ± standard deviation (SD) unless stated differently.

3.5 Results

3.5.1 Study selection

The initial search yielded a total 14,409 records including 82 papers that were selected through hand search and two more through cross reference. After removal of duplicates and title and abstract screening, a total of 112 articles were left for full-text assessment (*Fig. 9*). The authors of 5 out of these 112 articles were contacted at this stage in order to provide additional data on ARP dimensional outcomes before the final selection.

The most common reason for exclusion of papers was insufficient numbers of patient, no relevant outcome data, data which was relevant but recorded in a manner / format which was incompatible with the inclusion criteria, duplicate report, insufficient follow up time and the study design not matching research protocol. The excluded papers and the reasons for exclusion for both focused questions are listed in Table 20.

The Kappa score for agreement between the reviewers (Dr Anna Trullenque-Eriksson and Dr Neil MacBeth) at the title and abstract selection level was 0.95 indicating a high level of agreement.

Figure 9. *Selection process and search strategy flowchart for Systematic Review 2*

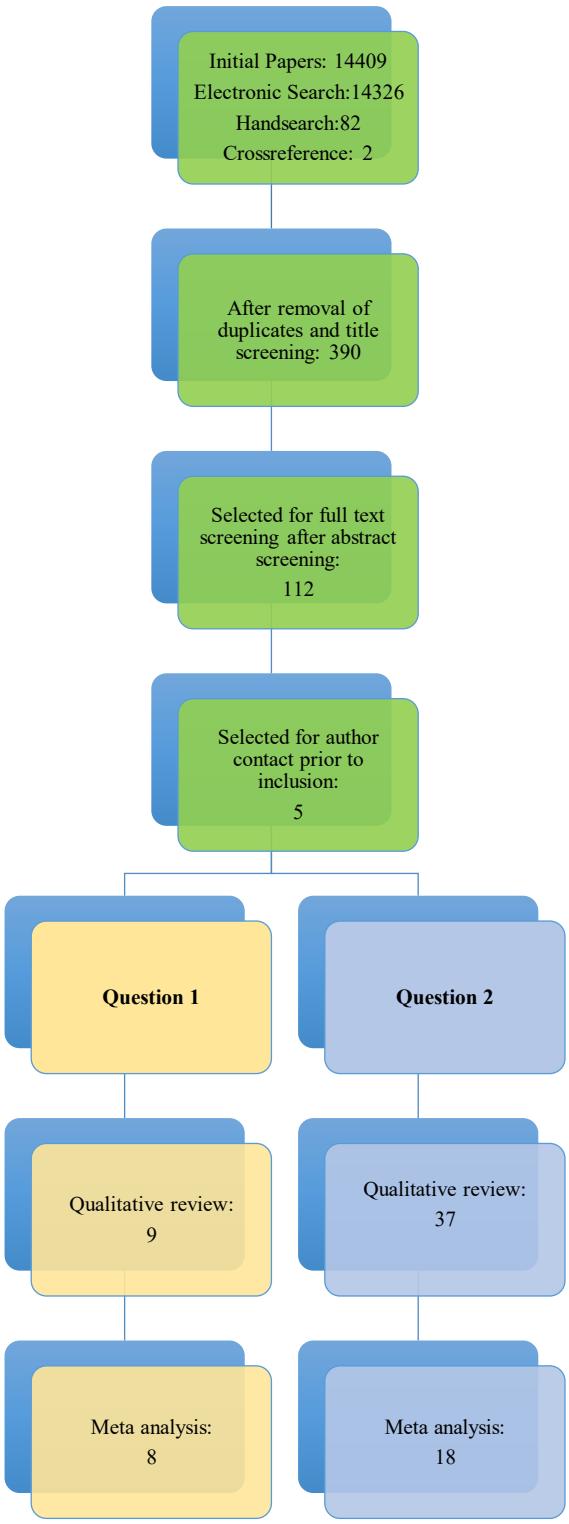


TABLE 20: *List of excluded full text papers and reasons for exclusion following full text screening*

Author and year	Reasons for exclusion
(Alkan et al., 2013)	Insufficient number of patients
(Al-Khaldi et al., 2011)	No relevant outcome data or data provided in incompatible format
(Anitua, 1999)	Insufficient number of patients
(Anitua, 1999)	No relevant outcome data or data provided in incompatible format, insufficient follow-up
(Araújo et al., 2015)	No relevant outcome data or data provided in incompatible format
(Artzi et al., 2000)	Insufficient number of patients
(Babbush, 2003)	Insufficient number of patients
(Barone et al., 2008)	Duplicate report (Barone 2012)
(Barone et al., 2012)	No relevant outcome data or data provided in incompatible format
(Brkovic et al., 2012)	Insufficient number of patients
(Brownfield and Weltman, 2012)	Insufficient number of patients
(Canullo et al., 2013)	Insufficient number of patients
(Canuto et al., 2013)	No relevant outcome data or data provided in incompatible format, insufficient follow-up
(Cardaropoli et al., 2012)	Duplicate report (Cardaropoli 2014)
(Carmagnola et al., 2003)	Insufficient number of patients
(Casado et al., 2010)	Insufficient number of patients
(Crespi et al., 2009b)	No relevant outcome data or data provided in incompatible format
(Clozza et al., 2012)	Duplicate report (Clozza 2014), insufficient number of patients
(Clozza et al., 2014)	Insufficient number of patients
(Collins et al., 2014)	Insufficient number of patients
(De Coster et al., 2011)	Insufficient number of patients, study seems to be retrospective
(Engler-Hamm et al., 2011)	Insufficient number of patients
(Farina et al., 2013)	No relevant outcome data or data provided in incompatible format
(Fotek et al., 2009)	Insufficient number of patients
(Flügge et al., 2015)	Unclear study design
(Geffre et al., 2010)	Animal study
(Geurs et al., 2014)	Insufficient number of patients
2014)	Study seems to be retrospective
(Hauser et al., 2013)	Insufficient number of patients
(Heberer et al., 2008)	Insufficient number of patients
(Heberer et al., 2011)	Insufficient number of patients
(Heberer et al., 2012)	Insufficient number of patients
(Hernandez-Alfaro et al., 2005)	Insufficient number of patients, reports on a mixture of clinical situations (ARP, discrepancy implant-socket, reconstruction after removal of implants, etc.)
(Hsuan-Yu et al., 2012)	Insufficient number of patients
(Irinakis, 2006)	Review article
(Jung et al., 2004)	No relevant outcome data or data provided in incompatible format, insufficient follow-up

(Kim et al., 2011a)	No relevant outcome data or data provided in incompatible format
(Kim et al., 2013)	Insufficient number of patients
(Kotsakis et al., 2014a)	Insufficient number of patients
(Kotsakis et al., 2014b)	Insufficient number of patients
(Lambert et al., 2012)	Insufficient number of patients
(Leblebicioglu et al., 2013)	No relevant outcome data or data provided in incompatible format
(Lekovic et al., 1998)	Duplicate report (Camargo 2000)
Luczyszyn et al., 2005)	Insufficient number of patients
(Madan et al., 2014)	Insufficient number of patients
(Mahesh et al., 2012)	Study design
(Mardas et al., 2010)	Duplicate report (Mardas 2010)
(Mardinger et al., 2009)	Duplicate report (Mardinger 2012)
(Misch, 2010)	Insufficient number of patients
(Moghaddas et al., 2012)	Insufficient number of patients
(Nam et al., 2011)	No relevant outcome data or data provided in incompatible format
(Neiva et al., 2011)	Insufficient number of patients
(Ntounis et al., 2015)	Insufficient follow-up
(Nevins et al., 2014a)	Insufficient number of patients
Norton and Wilson, 2002)	Insufficient number of patients
(Oghli and Steveling, 2010)	No relevant outcome data or data provided in incompatible format
(Patel et al., 2013)	Duplicate (Mardas 2010)
(Pellegrini et al., 2014)	Insufficient number of patients
(Ruga et al., 2011)	Insufficient number of patients
(Scheyer et al., 2012)	Insufficient number of patients
(Schneider et al., 2014)	Duplicate report (Jung 2013)
(Serino et al., 2008)	Insufficient number of patients
(Simon et al., 2011)	No relevant outcome data or data provided in incompatible format
(Sisti et al., 2012)	Insufficient follow-up
(Shakibaie, 2013)	Insufficient number of patients
(Spinato et al., 2014)	No relevant outcome data or data provided in incompatible format
(Suttapreyasri and Leepong, 2013)	Insufficient number of patients
(Tal, 1999)	Unclear study design and insufficient follow-up
(Tete et al., 2013)	Reports on a mixture of clinical situations (ARP vs sinus augmentation), insufficient follow-up
T(Thalmair et al., 2013)	Insufficient number of patients
(Toloue et al., 2012)	Unclear study design
(Vanhoutte et al., 2014)	Duplicate report (Lambert 2012)
(Villanueva-Alcojol et al., 2013)	Insufficient number of patients
(Weiss et al., 2007)	Insufficient number of patients
(Wu et al., 2014)	Insufficient number of patients

3.5.2 Study design and population

The study design and study population characteristics of the included studies for both focused questions are presented in Table 21.

Controlled Studies Answering the Focus Question 1

Nine papers (Aimetti et al., 2009, Barone et al., 2013a, Camargo et al., 2000, Cardaropoli et al., 2014, Festa et al., 2013, Fiorellini et al., 2005, Iasella et al., 2003, Jung et al., 2013b, Karaca et al., 2015) were eligible for inclusion in the qualitative analysis for focused question 1. Eight of the studies (Aimetti et al., 2009, Barone et al., 2013a, Cardaropoli et al., 2014, Festa et al., 2013, Fiorellini et al., 2005, Iasella et al., 2003, Jung et al., 2013b and Karaca et al., 2015) were designed as RCT trials, with one (Camargo et al., 2000) a CCT. Six of the studies were of a parallel design (Aimetti et al., 2009, Barone et al., 2013a, Cardaropoli et al., 2014, Fiorellini et al., 2005, Iasella et al., 2003 and Jung et al., 2013b), and three studies (Camargo et al., 2000, Festa et al., 2013 and Karacas et al., 2015) of a split mouth design. Five of the studies (Aimetti et al., 2009, Camargo et al., 2000, Festa et al., 2013, Fiorelini 2005 and Jung et al., 2013b) performed ARP utilising socket grafting procedures, three studies used GBR (Barone et al., 2013a, Cardaropoli et al., 2014 and Iasella et al., 2003) and one study, SS (Karacas et al., 2015).

Follow-up after ARP ranged from 3 to 6 months. Two studies (Aimetti et al., 2009 and Karacas et al., 2015) measured the dimensions of the post extraction alveolar ridge at 3 months, three (Barone et al., 2013a, Cardaropoli et al., 2014 and Forellini 2005) at 4 months, one at 4 and 6 months (Iasella et al., 2003) and the remaining three (Camargo et al., 2000, Festa et al., 2013 and Jung et al., 2013b) at 6 months.

All of the included studies measured alveolar and gingival tissue site dimensions using direct intra-oral measurements (Aimetti et al., 2009, Barone et al., 2013a, Camargo et al., 2000, Cardaropoli et al., 2014, Iasella et al., 2003 and Festa et al., 2013) or radiographic CBCT analysis (Corellini 2005, Jung et al., 2013b and Karacas et al., 2015).

Eight (Aimetti et al., 2009, Camargo et al., 2000, Cardaropoli et al., 2014, Festa et al., 2013, Fiorellini et al., 2005, Isella 2003, Jung et al., 2013b and Karacas et al., 2015) of the nine included studies prescribed pre- or post-operative antibiotics.

Five parallel studies (Aimetti et al., 2009, Barone et al., 2013a, Fiorellini et al., 2005, Iasella et al., 2003 and Jung et al., 2013b) were included in the meta-analysis. Cardaropoli et al., (2014) was excluded from the meta-analysis as the study used the socket as the unit of analysis, preventing pooling of data. A separate meta-analysis was carried out for the split mouth studies undertaken by Festa et al., (2013), Carmargo (2000) and Karacas et al., (2015).

The study population ranged from 15 to 80 patients in the included studies. This resulted in 194 patients being considered in the meta-analysis. 153 patients were present in parallel studies and 41 in the split mouth studies. The distribution of the extracted teeth included both single and multi-rooted teeth. Two of the studies included smokers (Jung et al., 2013b and Barone et al., 2013a,), two studies (Aimetti et al., 2009 and Festa 2013) excluded smokers and four (Camargo 2000, Fiorellini et al., 2005, Iasella et al., 2013 and Karacas et al., 2015) did not report on smoking habits.

Studies Answering the Focus Question 2

Thirty-seven studies (Aimetti et al., 2009, Barone et al., 2013a, Barone et al., 2013b, Barone et al., 2013c, Beck and Mealey, 2010, Borg and Mealey, 2015, Calasans-Maia et al., 2014, Camargo et al., 2000, Cardaropoli et al., 2014, Cook and Mealey, 2013, Coomes et al., 2013, Crespi et al., 2009a, Crespi et al., 2011a, Crespi et al., 2011b, Eskow and Mealey, 2014, Fernandes et al., 2011, Festa et al., 2013, Fiorellini et al., 2005, Gholami et al., 2012, Hoang and Mealey, 2012, Huh et al., 2011, Iasella et al., 2003, Jung et al., 2013b, Kim et al., 2014, Karaca et al., 2015, Lindhe et al., 2014, Mardinger et al., 2012, Meloni et al., 2015, Mardas et al., 2010, Perelman-Karmon et al., 2012, Pinho et al., 2006, Poulias et al., 2013, Serino et al., 2003, Vance et al., 2004, Wallace et al., 2013, Wood and Mealey, 2012) were included in the qualitative analysis of question 2. Twenty-nine studies (Aimetti et al., 2009, Barone et al., 2013a, Barone et al., 2013b, Barone et al., 2013c, Borg and Mealey 2010, Calasans- Maia 2014, Cardaropoli et al., 2014, Cook and Mealey 2013, Coomes et al., 2014, Crespi et al., 2011b, Eskow and Mealey 2014, Fernandes et al., 2011, Festa et al., 2013, Fiorellini et al., 2005, Gholami et al., 2012, Hoang and Mealey 2012, Huh et al., 2011, Iasella et al., 2003, Jung et al., 2013b, Kim et al., 2014, Karacas et al., 2015, Meloni et al., 2015, Neiva et al., 2008, Mardas et al 2010, Perelman-Karmon et al., 2012, Pinho et al., 2006, Poulias et al., 2013, Vance et al., 2004, (Wood and Mealey, 2012)) were designed as a RCT, seven studies (Beck and Mealey 2010, Crespi et al., 2009a, Crespi et al., 20011a, Carmago 2000, Lindhe et al., 2014, Serino et al., 2003 and Wallace et al., 2013) as a CCT and one study (Mardinger et al., 2012) was a prospective case series.

Eleven studies (Beck and Mealey 2010, Calasans-Maia et al., 2014, Coomes et al., 2014, Crespi et al., 2011a, Eskow and Mealey 2014, Fiorellini et al., 2005, Hoang and Mealey 2012, Huh et al., 2011, Jung et al., 2013b, Neiva et al., 2008 and (Wood and Mealey, 2012)) compared two different grafting techniques with seven studies (Aimetti et al., 2009, Crespi et al., 2009a, Crespi et al., 2001b, Festa et al., 2013, Cardaropoli et al., 2014, Iasella et al., 2003 and Serino et al., 2003) comparing a grafting procedure with unassisted socket healing. One study (Barone et al., 2013a) compared GBR with unassisted socket healing, twelve studies (Barone et al., 2013b, Barone et al., 2013c, Borg and Mealey 2015, Cook and Mealey 2013, Fernandes et al., 2011, Gholami et al., 2012, Kim et al., 2014, Mardas et al 2010, Perelman-Karmon et al., 2012, Pinho et al., 2006, Poulias et al., 2013 and Wallace et al., 2013) compared different GBR techniques. Four studies (Lindhe et al., 2014, Karacas et al., 2015, Mardinger

et al., 2012 and Meloni et al., 2015) compared different SS techniques, and one study (Vance et al., 2004) compared a grafting procedure against GBR. Finally, 3 studies (Crespi et al., 2009a, Fiorellini et al., 2005, Jung et al., 2013b) compared multiple grafting techniques against an unassisted healing control.

Follow-up times ranged from 3 to 9 months after the ARP. Seven studies (Aimetti et al., 2009, Barone et al., 2013c, Crespi et al., 2009a, Huh et al., 2011, Kim et al., 2014, Karacas et al., 2015 and Neiva et al., 2008) examined dimensions after 3 months of healing. Sixteen studies after 4- 6 months (Barone et al., 2013a, Beck and Mealey 2010, Borg and Mealey 2015, Cardaropoli et al., 2014, Cook and Mealey 2013, Coomes et al., 2014, Crespi et al., 2011a, 2011b, Eskow and Mealey 2014, Fiorellini et al., 2005, Iasella et al., 2003, Meloni et al., 2015, Poulias et al., 2003, Vance et al., 2004, Wallace et al., 2013 and (Wood and Mealey, 2012)), thirteen studies after 6-9 months (Barone et al., 2013b, Calason-Mania 2014, Carmago 2000, Fernandes et al., 2011, Festa et al.,2013, Gholami et al., 2012, Hoag and Mealey 2012, Jung et al., 2013b, Lindhe et al., 2014, Mardinger et al., 2012, Mardas et al 2010, Pinho et al., 2006 and Serino et al., 2003) and one study after 9 months (Perelman-karman 2012).

Twenty-eight of the studies measured alterations in site dimensions. Twenty two (Aimetti et al., 2009, Barone et al., 2013a, Barone et al., 2013c, Beck and Mealey 2010, Borg and Mealey 2010, Calasans-Maia 2014, Camargo et al., 2000, Cardaropoli et al., 2014, Cook and Mealey 2013, Eskow and Mealey 2014, Fernandes et al., 2011, Festa et al., 2013, Gholami et al., 2012, Hoang and Mealey 2012, Iasella et al., 2003, Karacas et al., 2015, Neiva et al., 2008, Mardas et al., 2010, Pinho et al., 2006, Poulias et al., 2013, Serino et al., 2003, Vance et al., 2004, (Wood and Mealey, 2012)) directly measured the alteration in the size of alveolar complex, with seven studies recording measurements from intra-oral (Crespi et al., 2009a) or CBCT (Fiorellini et al., 2005, Huh et al., 2011, Jung et al., 2013b, Kim et al., 2014, Karacas et al., 2015, Meloni et al., 2015) radiographic images. One study measured both intra-oral and radiographic measurements (Coomes et al., 2014). Seven studies (Barone et al., 2013b, Crespi et al., 2011a, 2011b, Lindhe et al., 2014, Mardinger et al., 2012, Perelmen-Karman 2012 and Wallace et al., 2013) did not attempt to measure dimensional changes of the hard tissues but provided either histological information or soft tissue changes.

Twenty-nine (Aimetti et al., 2009, Barone et al., 2013c, Beck and Mealey 2010, Borg and Mealey 2015, Calasans-Maia et al., 2014, Camargo et al., 2000, Cardaropoli et al., 2014, Cook and Mealey 2013, Coomes et al., 2014, Crespi et al., 2009a, Crespi et al., 2009b, Crespi et al., 2011a, Crespi et al., 2011b, Eskow and Mealey 2014, Fernandes et al., 2011, Festa et al., 2013, Gholami et al., 2012, Hoang and Mealey 2012, Iasella et al., 2003, Jung et al., 2013b, Kim et al., 2014, Karacas et al., 2015, Lindhe et al., 2014, Mardinger et al., 2012, Neiva et al., 2008, Mardas et al., 2010, Pinho et al., 2006, Vance et al., 2004, (Wood and Mealey, 2012)) of the thirty-seven included studies prescribed pre or post-operative antibiotics. Four studies (Barone et al., 2013a, Perelman-Karman 2012, Poulias et al., 2013-one group and Serino et al., 2003) did not prescribe AB as a component of treatment, and five studies

(Barone et al., 2013b, Huh et al., 2011, Neiva et al., 2008, Poulias et al., 2013-one group and Wallace et al., 2013) did not provide this information.

Eighteen studies were included in the meta-analysis (Aimetti et al., 2009, Barone et al., 2013a, Barone et al., 2013c, Borg and Mealey 2015, Calasans-Maia et al., 2014, Coomes et al., 2014, Fiorellini et al., 2005, Hoang and Mealey 2012, Huh et al., 2011, Iasella et al., 2003, Jung et al., 2013b, Kim et al., 2014, Meloni et al., 2015, Neiva et al., 2008, Mardas 2010, Poulias et al., 2013, Vance et al., 2004, (Wood and Mealey, 2012)). The study population ranged from 20 to 80 patients. Following categorisation into intervention groups, 266 patients were considered for the meta-analysis of *GBR* group, 317 patients for the meta-analysis of the *socket grafting* group and 50 patients for the meta-analysis of the SS group. Although the distribution of the teeth extracted in the *GBR* and *socket grafting* groups was fairly heterogeneous and included both single and multi-rooted teeth, the location of the extracted teeth in the *SS* group was mainly maxillary, non-molar teeth.

Seven of the studies included both smokers and non-smokers (Barone et al., 2013a, 2014, Coomes et al., 2014, Jung et al., 2013b, Meloni et al., 2015, Mardas et al., 2010 and Poulias et al., 2013), six (, Fiorellini et al., 2005, Hoang 2012, Huh et al., 2011, Iasella et al., 2003, Kim et al., 2014, and Vance et al., 2004) did not report on smoking habits, and five studies (Aimetti et al., 2009, Borg and Mealey 2015, Calasans-Maia et al., 2014 Neiva 2008 and Wood 2012) excluded smokers.

***Table 21**. Study characteristics of included papers, Systematic Review 2*

Reference	Setting (country, number, type centre)	Source of funding, reported conflict of interest	Study design	Who carried out procedures	Number of patients (sockets)	Mean age ± SD and/or range	Smokers included	Socket location and defect morphology	Materials (details, number of patients / sockets)	Atraumatic extraction	Flap raised	Primary closure	Pre- or post-operative antibiotics	Healing time before measurement / biopsy	Dimensions of ridge evaluated by
Aimetti 2009[‡§]	Italy, 1, U	Unclear	RCT, Parallel	Unclear	40 (40)	51.27 ± 8.40; 36 - 68	N	Anterior maxillary single-tooth; 4 walls	Grafting (CS; 22/22) vs unassisted healing (18/18)	Y	N	N	Y	3	Directly
Barone 2013a[‡§]	Italy, 1, H	Unclear	RCT, Parallel	Specialists	58 (58)	40.5; 20 - 63	Y	Molar or premolar	GBR (corticocancellous porcine bone + collagen barrier; 29/29) vs unassisted healing (29/29)	?	N	N	N	4	Directly
Barone 2013b*	Italy, Germany, Spain, 6, U and P?	Industry, Unclear	RCT, Unclear	Unclear	38 (62)	51 ± 14	Y	Molar or premolar; excluded if facial soft tissue and buccal plate markedly reduced	GBR (bovine xenograft + collagen barrier; ?/31; T1) vs GBR (bovine xenograft + collagen barrier; ?/31; T2)	Y	Y	N	?	6	-
Barone 2013c[§]	Italy, 1, H	Unclear, No	RCT, Parallel	Specialists	64 (64)	32.7 ± 12.4; 18 - 47	Y	Molar or premolar; 4 walls	GBR (corticocancellous porcine bone + collagen barrier; 32/32; T1) vs GBR (corticocancellous porcine bone + collagen barrier; 32/32; T2)	Y	T1: N T2: Y	T1: N T2: Y	Y	3	Directly
Beck 2010	USA, 1, U	Self-funded, Yes	CCT, Parallel	Unclear	33 (38)	57.4; 39 - 76	?	Single root; excluded if >50% of any socket wall absent	Grafting (non–freeze-dried cancellous mineralized human bone allograft + collagen; 19/22; T1) vs grafting (non–freeze-dried cancellous mineralized human bone allograft + collagen; 14/16; T2)	Y	N	N	Y	Approx 2.5 or approx 5.5	Directly
Borg 2015[§]	USA, Unclear, Unclear	Industry, Yes	RCT, Parallel	Specialists	42 (42)	52; 20-89	N	Single rooted tooth; excluded if >50% dehiscence	GBR (cortical mineralized FDBA + d-PTFE barrier; 20/20; T1) vs GBR (70% cortical mineralized FDBA / 30% cortical DFDBA + d-PTFE barrier; 21/21; T2)	Y	Y	N	Y	17 - 21 weeks (average 19 weeks)	Directly
Calasans-Maia 2014[§]	Brazil, 1, U	Unclear	RCT, Parallel	Unclear	20 (20)	44.55 ± 10.87; 23-60	N	Unclear	Grafting (DBBM; 10/10; T1) vs grafting (DBBM; 10/10; T2)	Y	Y	Y	Y	6	Directly
Camargo 2000[‡]	Unclear	Industry, Unclear	CCT, Split-mouth	Unclear	16 (32)	44 ± 15.9	?	Non-molar	Grafting (bioactive glass + CS; 16/16) vs unassisted healing (16/16)	Y	Y	N	Y	6	Directly
Cardaropoli 2014	Italy, 1, P	Unclear	RCT, Parallel	Unclear	41 (48)	47.2 ± 12.9	Y	Molar or premolar; 3 intact walls and at least 80% of fourth wall intact	GBR (bovine bone mineral blended with collagen + collagen barrier; 21/24) vs unassisted healing (20/24)	Y	T1: Y C: N	N	Y	4	Directly
Cook 2013	USA, 1, U	Industry, No	RCT, Parallel	Specialist trainees	38 (40)	56; 23 - 78	Y	Non-molar; excluded if bony dehiscence >50% of total socket depth	GBR (bovine bone mineral blended with collagen + collagen barrier; 20/21; T1) vs GBR (hydroxiapatite + collagen barrier; 18/19; T2)	Y	Y	N	Y	4 - 5	Directly
Coomes 2014[§]	USA, 1, U	Industry, Yes	RCT, Parallel	Unclear	34 (34)	19 - 79	Y	Buccal bone destruction	Grafting (collagen + rhBMP-2; 18/18; T1) vs grafting (collagen; 16/16; T2)	Y	N	N	Y	5	Both
Crespi 2009a*	Italy, 1, H	Unclear, No	CCT, Split-mouth	Specialists	15 (45)	51.3; 28 - 72	N	Molar or premolar; 3 bone walls and loss of buccal plate	Grafting (MHA + collagen; 15/15; T1) vs grafting (CS + collagen; 15/15; T2) vs unassisted healing (15/15)	?	N	N	Y	3	Other
Crespi 2011a*	Italy, 1, H	Unclear	CCT, Split-mouth	Specialists	15 (45)	53.7; 32 - 70	N	One molar or premolar on each side of jaw and one additional randomly located tooth to be used as a control	Grafting (MHA + collagen; 15/15; T1) vs grafting (corticocancellous xenogenic bone + collagen; 15/15; T2) vs grafting (collagen; 15/15; T3)	Y	N	N	Y	4	-

Crespi 2011b*	Italy, 1, H	Unclear	RCT, Split-mouth	Specialists	15 (30)	53.7; 32 - 70	N	One molar or premolar on each side of jaw; 3 bone walls and loss of buccal plate	Grafting (corticocancellous xenogenic bone + collagen; 15/15) vs unassissted healing (15/15)	?	T1: ? C: N	T1: N C: ?	Y	4	-
Eskow 2014*	USA, 1?, U	Unclear, No	RCT, Parallel	Unclear	35 (35)	54; 27 - 79	Y	Non-molar; excluded if >50% of socket wall's vertical dimension absent	Grafting (cortical FDBA + collagen; 17/17; T1) vs grafting (cancellous FDBA + collagen; 18/18; T2)	Y	N	N	Y	Approx. 4	Directly
Fernandes 2011	Brazil, 1, U	Unclear, No	RCT, Split-mouth	Unclear	18 (36)	33 - 58	?	Maxillary single-rooted teeth	GBR (anorganic bovine bone matrix with cell-binding peptide P-15 + acellular dermal matrix barrier; 18/18; T1) vs GBR (acellular dermal matrix barrier; 18/18; T2)	Y	Y	N	Y	6	Directly
Festa 2013[‡]	Italy, 1, U	Unclear, No	RCT, Split-mouth	Unclear	15 (30)	28 - 58	N	Premolars; excluded if buccal or palatal/lingual bony wall fractured/lost	Grafting (corticocancellous porcine bone + soft cortical membrane; 15/15) vs unassisted healing (15/15)	Y	Y	T1: N C: Y	Y	6	Directly
Fiorellini 2005[‡§]	USA?, 8, U	Industry, Yes	RCT, Parallel	Unclear	80 (95)	47.4	?	Non-molar maxillary teeth; buccal wall defects	Grafting (collagen sponge with human BMP-2; 22/?; T1) vs grafting (collagen sponge with BMP-2; 21/?; T2) vs grafting (collagen sponge; 17/?; T3) vs unassisted healing (20/?)	?	Y	Y	Y	4	CBCT
Gholami 2012	Iran, 1?, U?	Unclear	RCT, Split-mouth	Unclear	12 (28)	44.6 ± 11.4; 21-60	?	Non-molar; four-wall sockets	GBR (DBBM + collagen barrier; 12/14; T1) vs GBR (nanocrystalline HA embedded in silica gel matrix + collagen barrier; 12/14; T2)	Y	Y	Y	Y	6 - 8	Directly
Hoang 2012[§]	USA, 1, U	Self-funded, No	RCT, Parallel	Unclear	30 (30)	56.1; 29 - 76	?	Molar; excluded if buccal bony dehiscence >50% of length of socket	Grafting (demineralized bone matrix in a carrier of bovine collagen and sodium alginate + collagen; 16/16; T1) vs grafting (demineralized bone matrix in a carrier of bovine collagen and sodium alginate + collagen; 14/14; T2)	Y	?	N	Y	4 - 5	Directly
Huh 2011[§]	South Korea, 3, Unclear	Governmental, Unclear	RCT, Parallel	Unclear	72 (72?)	52.77 ± 6.71; 35-65	?	Premolar or molar; <50% localized alveolar vertical bone loss	Grafting (β-TCP/HA + ErhBMP-2 ; 36/?; T1) vs grafting (β-TCP/HA; 36/?; T2)	?	?	?	?	3	CBCT
Iasella 2003[‡§]	Unclear	Unclear	RCT, Parallel	Unclear	24 (24)	51.5; 28 - 76	?	Non-molar	GBR (FDBA + collagen barrier; 12/12) vs unassisted healing (12/12)	Y	Y	N	Y	4 or 6	Directly
Jung 2013b[‡]	Switzerland, 2 centres in 1 U	Institutional and industry, No	RCT, Parallel	Unclear	40 (40)	Per groups: 48 ± 15; 59 ± 11; 65 ± 13; 49 ± 14	Y	Excluded if >50% buccal bone height lost	Grafting (β-TCP particles with poly(lactideco-glycolide) coating; 10/10; T1) vs sealing (DBBM with 10% collagen + porcine collagen matrix (Mucograft); 10/10; T2) vs sealing (DBBM with 10% collagen + autogenous soft tissue graft; 10/10; T3) vs unassisted healing (10/10)	Y	?	T1; N T2: Y T3: Y C: N	Y	6	CBCT
Karaca 2015[‡]	Turkey, 2?, U?	Self-funded	RCT, Split-mouth	Unclear	10 (20)	46.7; 36 - 60	?	Maxillary anterior teeth	Sealing (free gingival graft from palate; 10/10) vs unassisted healing (10/10)	Y	N	T: Y C: N	Y	3	CBCT
Kim 2014[§]	South Korea, 2, U	Institutional, Unclear	RCT, Parallel	Unclear	59 (59)	Control 51.18 ± 10.14; experimental 50.37 ± 13.45	?	Non-molar; <50% bone loss in all dimensions.	GBR (demineralized human bone matrix + rhBMP-2 + collagen barrier; 29/29; T1) vs GBR (demineralized human bone matrix + rhBMP-2 + collagen barrier; 30/30; T2)	Y	Y	?	Y	3	CBCT
Lindhe 2014*	Unclear	Unclear	CCT, Parallel	Unclear	24 (24)	25 - 54	?	Excluded if buccal dehiscence defect ≥2 mm	Sealing (DBBM + Mucograft®; 13/13; T1) vs sealing (Mucograft®; 11/11; T2)	Y	N	Y	?	6	-
Mardinger 2012*	Israel, Unclear, U and P	Unclear	Prospective case series, Non-controlled	Unclear	36 (43)	50.75; 24 - 75	Y	Site not completely surrounded by bony walls; excluded if less than two bony wall defects	Sealing (porous bovine xenograft + intrasocket reactive soft tissue; 36/43)	Y	N	Y	Y	6	-

Meloni 2015	Italy, 2, P	Unclear, No	RCT, Parallel	Specialists	30 (30)	48; 26-72	Y	Maxillary non-molar; excluded if fenestration or dehiscence ≥ 3 mm	Sealing (DBBM + epithelial connective tissue graft from palate; 15/15; T1) vs Sealing (DBBM + porcine collagen matrix; 15/15; T2)	Y	N	Y	Y	5	CBCT
Neiva 2008[§]	USA, 1, U	Industry, No	RCT, Parallel	Specialists	24 (24)	25 - 76	N	Maxillary premolars with >80% bone volume in all dimensions	Grafting (anorganic bovine-derived HA matrix combined with a synthetic cellbinding peptide P-15 + collagen; 12/12; T1) vs grafting (collagen; 12/12; T2)	Y	N	N	?	3.7	Directly
Patel 2013[§]	United Kingdom, 1, U	Industry, Unclear	RCT, Parallel	Specialists	26 (26)	37.3 ± 11.4; 20 - 58	Y	Non-molar; excluded if major part of buccal or palatal wall damaged or lost	GBR (60% HA + 40% b-tricalcium phosphate + collagen barrier; 13/13; T1) vs GBR (DBBM + collagen barrier; 13/13; T2)	Y	Y	N	Y	8	Directly
Perelman-Karmon 2012*	Unclear	Unclear	RCT, Parallel	Unclear	23 (23)	26 - 68	N	Non-molar; at least 50% of sockets partially resorbed/ destructed at one to two walls, but not circunferentially	GBR (bovine bone mineral + collagen barrier; 11/11; T1) vs grafting (bovine mineral bone; 12/12; T2)	?	Y	Y	N	9	-
Pinho 2006	Brazil, 1, U	Unclear, No	RCT, Split-mouth	Unclear	10 (20)	46.3; 35-60	N	Maxillary non-molar	GBR (autograft + titanium barrier; 10/10; T1) vs GBR (titanium barrier; 10/10; T2)	Y	Y	Y	Y	6	Directly
Poulias 2013[§]	USA, 1, U	Self-funded, No	RCT, Parallel	Specialist trainees	23 (23)	52 ± 16; 26 - 77	Y	Non-molar	GBR (cancellous allograft + resorbable polylactide barrier; 12/12; T1) vs GBR (cancellous allograft + bovine xenograft + resorbable polylactide barrier; 11/11; T2)	Y	Y	N	T1: N T2: ?	4	Directly
Serino 2003*	Unclear	Unclear	CCT, Unclear	Unclear	36 (39)	35 - 64	?	Unclear	Grafting (polylactide-polyglycolide acid sponge; 24/26) vs unassisted healing (12/13)	?	Y	?	N	6	Directly
Vance 2004[§]	Unclear	Industry, Unclear	RCT, Parallel	Unclear	24 (24)	56	?	Non-molar	Grafting (carboxymethylcellulose + CS + DFDBA; 12/12; T1) vs GBR (bovine bone mineral + collagen barrier; 12/12; T2)	Y	Y	N	Y	4	Directly
Wallace 2013*	Unclear	Industry, Yes	CCT, Parallel	Unclear	30 (34)	18 - 70	N	18 intact and 16 sockets with buccal wall defects	GBR (allograft + rhPDGF-BB + resorbabe acellular dermal matrix barrier; ?/19; T1) vs GBR (allograft + saline + acellular dermal matrix barrier; ?/15; T2)	Y	Y	Y	?	4	-
Wood 2012[§]	USA, 1, U	Industry, No	RCT, Parallel	Specialist trainees	33 (33)	56.7; 20 - 78	N	Single-rooted non-molar	Grafting (DFDBA + collagen; 17/17; T1) vs grafting (FDBA + collagen; 16/16; T2)	Y	?	N	Y	4 - 4.7	Directly

All studies included for Question 2; highlighted studies included for Question 1
*[†] = selected for meta-analysis Question 1 [§] = selected for meta-analysis Question 2 * = included only for histologic data*
U = university H = hospital P = private practice Y = yes N = no ? = unclear RCT = randomised clinical trial CCT = controlled clinical trial GBR = guided bone regeneration T1 = test group 1 T2 = test group 2 T3 = test group 3 C = control group
MHA = magnesium-enriched hydroxyapatite CS = calcium sulphate FDBA = freeze-dried bone allograft DBBM = deproteinized bovine bone mineral HA = hydroxyapatite DFDBA = demineralized freeze-dried bone allograft d-PTFE = dense polytetrafluoroethylene
β-TCP = Beta-tricalcium phosphate

3.5.3 Intervention characteristics

The interventional characteristics of the included studies for both focused questions are presented in Table 21.

3.5.3.1 Controlled studies answering the focused question 1

In four out of the nine included studies (Camargo et al., 2000, Festa et al., 2013, Fiorellini et al., 2005 and Iasella et al., 2003), muco-periosteal flaps were elevated both at the ARP treated and control extraction sites. In one paper (Cadaropoli 2014), a flap was only raised in the treatment group. In the remaining four studies (Aimetti et al., 2009, Barone et al., 2013a, Karacas et al., 2015 and Jung et al., 2013b), a flapless approach was followed. Primary closure was attempted in both the treatment and control groups in one study (Fiorellini et al., 2005), with one study (Jung et al., 2013b) undertaking primary closure in two of three treatment groups and one study (Festa et al., 2013) only in the control group. In the five studies that specified the number of intact walls at the extraction site, all had at least 3 walls intact after extraction of the tooth (Aimetti et al., 2009, Cardaropoli et al., 2014, Festa et al., 2013, Fiorellini et al., 2005 and Jung et al., 2013b).

In three out of the nine included studies, ARP was performed using a collagen barrier for GBR in combination with a porcine xenograft (Barone et al., 2013a, Cardaropoli et al., 2014) or an allograft (Iasella et al., 2003). In three studies, socket grafting was undertaken using an alloplast calcium sulphate or calcium phosphate (Aimetti et al., 2009, Jung et al., 2013b) and bioactive glass (Camargo et al., 2000). In one study a porcine xenograft with a porcine cortical layer was used for grafting of the sockets (Festa et al., 2013), in another study a polylactide-polyglycolide acid sponge and human BMP was provided (Fiorellini et al., 2005). Two SS techniques were examined against a socket grafting technique in one study (Jung et al., 2013b), with the effects of a porcine collagen matrix seal compared against a connective tissue graft. One study (Karacas et al., 2015) examined the effects of SS using a free gingival graft.

3.5.3.2 Studies answering the focused question 2

GBR

In seven out of the ten included studies (Borg and Mealey 2015, Iasella et al., 2003, Kim et al., 2014, Mardas et al., 2010, Poulias et al., 2013, Vance et al., 2004, Fernandes et al., 2011 and Pinho et al., 2006), muco-periosteal flaps were elevated as a component of the surgery. Two studies adopted a flapless surgical technique (Barone et al., 2013a and Barone et al., 2013c – one group). Pinho et al., (2006) and Barone et al., (2013c - one group) attempted primary closure at the tooth extraction site following GBR augmentation.

In the four studies that specified the number of intact walls required for inclusion in the study, all had at least 3 walls of the socket walls remaining intact, with greater that 50% of the 4th wall remaining after extraction of the tooth (Barone et al., 2013c, Borg and Mealey 2015, Kim et al., 2014 and Mardas et al., 2010).

GBR was performed in most of the studies using a collagen barrier for GBR in combination with either a porcine or bovine xenograft (Barone et al., 2013a, Barone et al., 2013c, Mardas et al., 2010– one group and Vance et al., 2004), hydroxyapatite (Cook and Mealey et al., 2013-one group, Gholami et al., 2012- one group), synthetic ceramic (Mardas et al., 2010 –one group), or freeze dried bone allograft (Borg and Mealey 2015-PTFE membrane, Iasella et al., 2003, Kim et al., 2014, Poulias et al., 2013 and Vance et al., 2004–one group). One study (Pinho et al., 2006) used an autograft harvested from the maxillary tuberosity in combination with a titanium barrier. An acellular dermal matrix barrier in combination with an acellular dermal matrix allograft was used by (Fernandes et al., 2011), and a resorbable polylactide barrier with cancellous allograft with or without bovine xenograft was used by Poulias et al., (2013).

Socket Grafting

In five out of the twelve included studies (Calasans-Maia et al., 2014, Camargo et al., 2000, Festa et al., 2013, Fiorellini et al., 2005, Vance et al., 2004) muco-periosteal flaps were elevated as a component of the surgery. Four studies adopted a flapless surgical technique (Aimetti et al., 2009, Coomes et al., 2014, Jung et al., 2013b and Neiva et al., 2008). It was unclear whether flaps were elevated in three studies (Hoang and Mealey 2012, Huh et al., 2011 and (Wood and Mealey, 2012)). Primary tissue closure was attempted in four of the studies (Calasans-Maia et al., 2014, Fiorellini et al., 2005, Jung et al., 2013b-two groups and Festa et al., 2013-one group), with only one group in one study not specifying the surgical technique (Huh et al., 2011). In all other groups, primary closure was not attempted.

In the eight studies that specified the number of intact walls required for inclusion in the study, all required at least 3 walls of the socket wall remaining intact, with greater that 50% of the fourth wall remaining after extraction of the tooth (Aimetti et al., 2009, Coomes et al., 2014, Festa et al., 2013, Fiorellini et al., 2005, Hoang and Mealey 2012, Jung et al., 2013b and Neiva et al., 2008).

Socket grafting was performed using either allografts (Calasans-Maia et al., 2014), xenografts (Festa et al., 2013, Vance et al., 2004-one group), xenografts combined with a synthetic collagen peptide collagen known as P-15 (Neiva et al., 2008-one group), alloplasts and bioactive glass materials (Aimetti et al., 2009, Camargo et al., 2000, Jung et al., 2013b-one group), a combination of alloplasts, xenografts and rhBMP-2 (Huh et al., 2011), a combination of allograft and collagen (Wood and Mealey, 2012), a combination of synthetic polymer, ceramic material and allograft (Vance et al., 2004-one group), a demineralized xenograft matrix in bovine collagen and sodium alginate carrier (Hoang and Mealey et

al., 2012) and a collagen carrier with and without rhBMP-2 (Coomes et al., 2014 and Fiorellini et al., 2005).

SS Studies

All three included studies (Karacas et al., 2015, Meloni et al., 2015 and Jung et al., 2013b) adopted a flapless surgical technique. Two of these studies required patients to have at least 3 walls of the socket walls intact, with the fourth wall having greater than 50% of the buccal bone remaining or a dehiscence or fenestration of less than 3mm. No description of the socket wall morphology was provided by Karacas et al., (2015).

Both Meloni et al., (2015) and Jung et al., (2013b) examined the effects of SS using a bone allograft and either a connective tissue (Meloni et al., 2015) or free gingival graft (Jung et al., 2013b) in comparison to ARP using an allograft and porcine collagen matrix. The allograft in the Jung et al., (2013b) study was a deproteinized bovine bone mineral with 10% collagen. Karacas et al., (2015) examined the isolated effect of using a free gingival graft for SS.

3.5.4 Outcome variables

The outcomes for the collected data, for both **Focused Question 1 and Focused Question 2** are presented in Table 22.

3.5.4.1 Outcome of controlled studies answering focused question 1

a) Linear and Volumetric Changes in Vertical Alveolar Bone Height (Mid-Buccal)

Parallel Studies: Five studies (*Fig. 10*) reported on changes in the mid-buccal vertical alveolar ridge height dimensions (Aimetti et al., 2009, Barone et al., 2013a, Cardaropoli et al., 2014, Iasella et al., 2003 and Jung et al., 2013b). There was a moderate level of heterogeneity (I^2= 55.33%, p=0.0839). The standardised mean difference (SMD) in vertical mid-buccal bone height (mm) between ARP and non-treated extraction sites was 0.739mm (95% CI: 0.332 to 1.147). The difference between the ARP and control group was found to be statistically significant (p<0.001).

Split-mouth Studies: Three studies (*Fig. 10*) reported data on changes in the mid-buccal vertical alveolar ridge dimensions (Camargo et al., 2000, Festa et al., 2013 and Karacas et al., 2015). There was a high level of heterogeneity (I^2= 76.18%, p = 0.015). The standardised mean difference (SMD) in vertical mid-buccal bone height (mm) between ARP and non-treated extraction sites was 0.975mm (95% CI: 0.017 to 1.933). The difference between the ARP and control group was found to be statistically significant (p=0.046).

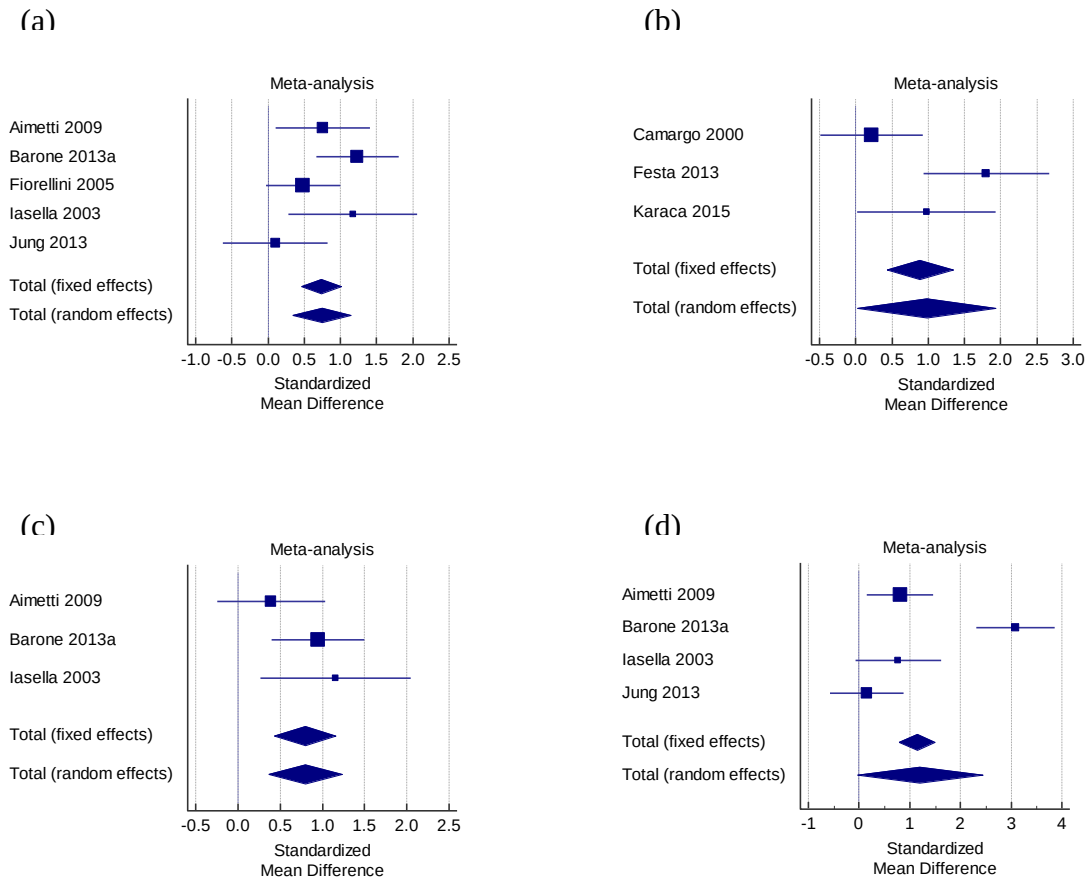


Figure 10*. Meta-analysis results and heterogeneity test for Q1; parallel studies, (a) parallel studies investigating linear and volumetric changes in vertical alveolar bone height (Mid-Buccal), (b) split mouth studies reporting on changes in the mid-buccal vertical alveolar ridge dimensions, (c) parallel studies investigating linear and volumetric changes in vertical alveolar bone height (proximal), (d) parallel studies investigating linear and volumetric changes in alveolar bone width.*

b) Linear and Volumetric Changes in Vertical Alveolar Bone Height (Proximal)

Parallel studies: Three studies (*Fig. 10*) reported data on changes in the proximal vertical alveolar ridge dimensions (Aimetti et al., 2009, Barone et al., 2013a and Iasella et al., 2003). There was a low level of heterogeneity (I^2= 24.53%, p=0.2658). The SMD proximal vertical bone height between ARP and non-treated extraction sites was 0.796 mm (95% CI: 0.364 to 1.228). The difference between the ARP and control group was found to be statistically significant (p<0.001).

Split mouth studies: Only one study (Festa et al., 2013), reported on proximal bone changes in a split mouth study. The mean change in proximal vertical bone height was -0.3 ± 0.8 mm in the test group

and -0.4mm ± 1.2 in the control group. The difference between the measurements was not found to be statistically significant.

c) Linear And Volumetric Changes in Alveolar Bone Width

Parallel studies: Four studies (*Fig. 10*) reported data on changes in the horizontal alveolar ridge dimensions (Aimetti et al., 2009, Barone et al., 2013a, Iasella et al., 2003 and Jung et al., 2013b). There was a high level of heterogeneity (I^2= 91.37%, P < 0.0001). The SMD in the horizontal bone width (mm) between ARP and non-treated extraction sites was 1.198mm (95% CI: -0.0374 to 2.433). The difference between the ARP and control groups was not found to be statistically significant (p=0.057).

***Split mouth studies*:** Two studies reported on changes in the horizontal bone measurements. There was a high level of heterogeneity (I2= 89.50%, p=0.002). An SMD of -0.161 (95% CI: -0.866 to 0.544) was calculated for Camargo et al., (2000) and of 1.478 (95% CI: 0.652 to 2.304) for Festa et al., (2013).

d) Histological Characteristics of New Bone Formation

Three studies (Aimetti et al., 2009, Fiorellini et al., 2005 and Iasella et al., 2003) reported on the histological composition of trephined bone core samples after ARP procedures. Aimetti et al., (2009) and Fiorellini et al., (2005) examined the differences in the trabecular bone levels following socket grafting procedures using alloplastic and xenograft/bioactive materials. Aimetti et al., (2009) found 100% of living bone in the bone sample following calcium sulphate socket grafting, with 58.8% (SD ± 3.3) trabecular bone in the test group and 47.2% (SD ± 7.7) in the control group. The difference in the bone content was found to be statistically significant (p<0.001). Greater levels of lamellar bone were found in the test group at coronal and apical sites, with higher levels of woven bone found at the same level in the control group. No inflammation was recorded in either the test or control group samples. Although Fiorellini et al., (2005) did not report on the exact percentage of new bone formation for the different xenograft materials used, two-thirds of all the collected samples in each test group was found to be trabecular bone. No evidence of residual collagen matrix was found in the test groups, with no difference recorded between the native and induced bone observed. Iasella et al., (2003) found more bone formation in the test group treated with FDBA and a collagen membrane (65 ±10%) when compared to the unassisted socket healing controls (54%±12). In the test group, 28% vital and 37% non-vital FDBA fragments were observed. The residual FDBA particles were often surrounded by woven bone or occasionally encapsulated in fibrous connective tissue. The core samples examined by Fiorellini et al., (2005) and Iasella et al., (2003), did not demonstrate the presence of an inflammatory cellular response within the augmented bone.

e) Changes in Keratinised Tissue Width and Thickness

Three studies reported on the change in the keratinised tissue characteristics following ARP, two studies (Barone et al., 2013a and Festa et al., 2013) following a GBR procedure and one (Iasella et al., 2003) following socket grafting (Table 22). Barone et al., (2013a) reported an increase in the width of the keratinised tissue in both the test and control group (1.14 ± 0.8mm and 0.73 ± 0.8mm), with the test group having a greater shift of the gingival tissue towards the occlusal direction after ARP. Iasella et al., (2003) found that a loss in the gingival tissue thickness of -0.1 (SD ± 0.5) mm occurred following GBR using a collagen membrane and allograft material, with a tissue gain of 0.4 (SD ± 0.6) mm in the unassisted control group. The difference between the test and control group was found to be statistically significant ($p<0.05$). Festa et al., (2013) reported on the gingival tissue height following socket grafting using a combination of porcine xenograft and cortical membrane. This study indicated no change to the free gingival margin at the neighbouring teeth following tooth extraction in the test and the control group.

f) Post-Operative Complications and Patient-based Outcomes

All nine of the included studies reported on the occurrence of adverse events (Table 22). Five studies (Aimetti et al., 2009, Barone et al., 2013a, Camargo et al., 2000, Festa et al., 2013, and Jung et al., 2013b) reported no adverse events during the healing phase in the ARP test and control groups. One study did not provide any information on complications (Iasella et al., 2003). Three studies (Cardaropoli et al., 2014, Fiorellini et al., 2005 and Karacas et al., 2015) reported a high level of complications in both interventional and control groups, mainly oedema, oral pain and erythema in both the test and control groups. Fiorellini et al., (2005) and Karacas et al., (2015) found that the frequency of these complications were greater in the ARP groups. No studies reported on other variables associated with the patient experience in the test or the control groups.

3.5.4.2 Outcome of controlled studies answering focused question 2

GBR

a) Linear and Volumetric Changes in Vertical Alveolar bone Height (Mid-Buccal)

Meta-analysis of seven studies and eleven subgroups calculated a pooled effect size of -0.467 mm (95% CI: -0.866 to -0.069) reduction in the mid-buccal alveolar ridge height. The degree of variance in the studies was high. Allograft ARP appeared to be associated with a greater range of dimensional change (Borg and Mealey 2015, Iasella et al., 2003 and Poulias et al., 2013).

b) Proximal Vertical Bone Change

Meta-analysis of six studies and nine subgroups calculated an effect size of -0.356 mm (95% CI: -0.490 to -0.222) reduction in the proximal vertical bone height. The degree of variance in the studies was moderate.

c) Horizontal Change

Eight studies with 13 subgroups calculated a pooled effect size of -1.45 mm (95% CI: -1.892 to -1.008) reduction in the horizontal bone width. The degree of variance in the studies was high.

Socket Grafting

a) Vertical Mid-buccal Bone Changes

Nine studies, with sixteen subgroups calculated a pooled effect size of -0.157mm (95% CI: -0.554 to 0.239) reduction in the vertical bone height. The degree of variance in the studies was high. Two studies (Coomes et al., 2014 and Neiva et al., 2008) reported positive vertical height changes when the socket graft was covered with a xenograft collagen sponge.

b) Proximal Vertical Bone Changes

Only two groups from two studies (Aimetti et al., 2009 and Vance et al., 2004) reported on proximal vertical bone changes following SS procedures. Meta-analysis was therefore not attempted. A proximal vertical bone height change of -0.2 mm was calculated for Aimetti et al., 2009 (95% CI: -0.451 to 0.051) and -0.2 mm for Vance et al., 2004 (95% CI: -0.596 to 0.196).

c) Horizontal Bone Changes: Eight studies and thirteen subgroups calculated a pooled effect size reduction in the horizontal bone dimension of -1.613 mm (95% CI: -1.989 to -1.238). The degree of variance in the studies was moderate.

e) Dimensional changes: Only two eligible studies (Jung et al., 2013b and Meloni 2015) reported on dimensional bone changes following ARP with SS. Their results were found to be divergent. Jung et al., (2013b) reported a vertical change of 0 ± 1.2 mm and a width reduction of -1.2 ± 0.8 mm following SS with a porcine collagen matrix (Mucograft®) and a vertical height gain of 1.2 ± 2.9 mm and a horizontal reduction of -1.4 ± 1 mm following SS with a free gingival graft. Meloni et al., (2015) reported a height reduction of -1.6 ± 0.69 mm and width reduction of -0.54 ± 0.25 mm with a porcine collagen matrix, and height reduction of -1.47 ± 0.58 mm and -0.67 ± 0.31 mm width reduction when using a connective tissue graft. Both studies did not report a statistical difference between the two SS interventional groups.

f) Changes in Keratinised Tissue Width and Thickness

Seven groups from five studies (Barone et al., 2013a, Barone et al., 2013c, Festa et al., 2013, Iasella et al., 2003 and Vance et al., 2004) reported on keratinised tissue dimensions or gingival tissue thickness following ARP procedures (Table 22). Five groups from four studies (Barone et al., 2013a, Barone et al., 2013c, Iasella et al., 2003 and Vance et al., 2004) had undergone GBR, with two groups from two studies (Vance et al., 2004 and Festa et al., 2013) socket grafting procedures.

Two studies (Barone et al., 2013a and 2013c) reported on an increase in the width of keratinised tissue of, respectively, 1.14 ± 0.8 mm and 1.18 ± 0.8 mm when GBR procedures were performed. Barone et al., (2013c) indicated a reduction in keratinised tissue width -1.7 ± 0.6 mm when a GBR technique was combined with a coronally advanced flap for primary closure. Festa et al., (2013) did not report a change to the keratinised tissue margin when a socket grafting procedure was undertaken.

The thickness of the keratinised tissue margin was reported to be reduced -0.1 ± 0.5 mm (Iasella et al., 2003) and -0.2 ± 1.5 mm (Vance et al., 2004) when GBR procedures were undertaken. An increase in thickness was reported in a combination grafting procedure (Vance et al., 2004) 0.1 ± 0.6 mm.

Vance et al., (2004) reported on a reduction -0.1 ± 0.7mm in the lingual keratinised tissue when a socket grafting procedure was performed but no changes were observed (0.0 ± 0.7mm) when using a GBR procedure.

***Table 22**. Study Outcomes of Included Papers (I)*

Reference	Comparison	Changes in vertical alveolar ridge dimensions - midbuccal	Changes in vertical alveolar ridge dimensions – proximal	Changes in horizontal alveolar ridge dimensions	Histology (%)	Changes in keratinised tissues dimensions
Aimetti 2009[i§]	Grafting vs unassisted healing	T -0.5 ± 1.1 C -1.2 ± 0.6	T -0.2 ± 0.6 C -0.5 ± 0.9	T -2 ± 1.1 C -3.2 ± 1.8	T 58.8 ± 3.5 trabecular bone area fraction C 47.2 ± 7.7 trabecular bone area fraction	-
Barone 2013a[i§]	GBR vs unassisted healing	T -1.1 ± 0.96 C -2.1 ± 0.6	T -0.3 ± 0.76 C -1 ± 0.7	T -1.6 ± 0.55 C -3.6 ± 0.72	-	*Changes in width of keratinized gingiva* T +1.14 ± 0.8 C +0.73 ± 0.8
Barone 2013b*	GBR (T1) vs GBR (T2)	-	-	-	T1 28.5 ± 20 VB T2 31.4 ± 18.1 VB	-
Barone 2013c[§]	GBR (T1) vs GBR (T2)	T1 -1.1 ± 0.9 T2 -0.6 ± 0.7	T1 -0.3 ± 0.7 T2 -0.4 ± 0.5	T1 -1.7 ± 0.6 T2 -3.5 ± 0.9	-	*Changes in width of keratinized gingiva* T1 +1.8 ± 0.8 T2 -1.7 ± 0.6
Beck 2010	Grafting (T1) vs grafting (T2)	*Data per socket* T1 0.32 ± 2.61 T2 -0.37 ± 1.46	-	*Data per socket* T1 -1.43 ± 1.89 T2 -1.47 ± 1.89	T1 45 ± 19.8% new VB; 41.3 ± 14.6% CT; 13.5 ± 12.2% RGM T2 45.8 ± 22.4% new VB; 39.6 ± 13.0% CT; 14.6 ± 12.9% RGM	-
Borg 2015[§]	GBR (T1) vs GBR (T2)	T1 -0.25 ± 1.85 T2 0.26 ± 2.08	-	T1 -1.63 ± 1.18 T2 -1.19 ± 1.36	T1 24.69 ± 15.92 VB; 27.04 ± 13.62 RGM; 48.27 ± 14.16 CT/other T2 36.16 ± 11.91 VB; 18.24 ± 12.47 RGM; 45.38 ± 11.09 CT/other	-
Calasans-Maia 2014[§]	Grafting (T1) vs grafting (T2)	-	-	T1 -0.29 ± 0.14 T2 -0.39 ± 0.14	T1 33.6 ± 7.1 new VB area fraction; 32.3 ± 8.8 CT; 10.6 ± 16.2 RGM T2 19.3 ± 22.5 new VB area fraction; 49.9 ± 14 CT; 22.5 ± 7.9 RGM	-
Camargo 2000[i]	Grafting vs unassisted healing	T -0.38 ± 3.18 C -1 ± 2.25	-	T -3.48 ± 2.68 C -3.06 ± 2.41	-	-
Cardaropoli 2014	GBR vs unassisted healing	*Data per socket* T -0.56 ± 0.45 C -1.67 ± 0.43	-	*Data per socket* T -0.71 ± 0.91 C -4.04 ± 0.69	-	-
Cook 2013	GBR (T1) vs GBR (T2)	*Data per socket* T1 -0.14 ± 2.21 T2 0.03 ± 2.81	-	*Data per socket* T1 -1.57 ± 1.21 T2 -1.16 ± 1.44	T1 32.8 ± 14.7 bone; 13.4 ± 11.6 RGM; 53.7 ± 6.8 CT/other T2 47 ± 9.1 bone; RGM not detected; 53 ± 9.1 CT/other	-
Coomes 2014[§]	Grafting (T1) vs grafting (T2)	T1 4.75 ± 2.65 T2 1.85 ± 3.58	-	T1 -2.07 ± 1.17 T2 -3.4 ± 1.73	-	-
Crespi 2009a*	Grafting (T1) vs grafting (T2) vs unassisted healing	-	-	-	T1 40 ± 2.7 VB; 41.3 ± 1.3 CT; 20.2 ± 3.2 RGM T2 45 ± 6.5 VB; 41.5 ± 6.7 CT; 13.9 ± 3.4 RGM C 32.8 ± 5.8 VB; 64.6 ± 6.8 CT	-
Crespi 2011a*	Grafting (T1) vs grafting (T2) vs grafting (T3)	-	-	-	T1 36.5 ± 2.6 VB; 33.3 ± 1.5 CT; 32.2 ± 3.2 RGM T2 38.0 ± 16.2 VB; 25.3 ± 9.4 CT; 36.6 ± 4.8 RGM T3 30.3 ± 4.8 VB; 58.3 ± 7.1 CT	-
Crespi 2011b*	Grafting vs unassissted healing	-	-	-	T 39.6 ± 9.4 VB; 26.0 ± 9.9 CT; 34.4 ± 5.1 RGM C 29.5 ± 5 VB; 57.7 ± 6.9 CT	-
Eskow 2014*	Grafting (T1) vs grafting (T2)	-	-	-	*Mean (range)* T1 16.1 (12.1 to 30.3) new bone; 28.4 (18.5 to 37.5) RGM; 52.9 (47.4 to 57.1) CT/other T2 13 (10.1 to 31) new bone; 19.9 (15.8 to 24.3) RGM; 62.8 (50.9 to 68.5) CT/other	-
Fernandes 2011	GBR (T1) vs GBR (T2)	T1 -1.2 ± 2 T2 -1.5 ± 1.2	-	T1 -2.5 ± 1.8 T2 -3.4 ± 1.4	-	-
Festa 2013[‡]	Grafting vs unassisted healing	T -0.6 ± 1.4 C -3.1 ± 1.3	T -0.3 ± 0.8 C -0.4 ± 1.2	T -1.8 ± 1.3 C -3.7 ± 1.2	-	No changes to keratinised margin
Fiorellini 2005[i§]	Grafting (T1) vs grafting (T2) vs grafting (T3) vs unassisted healing	T1 -0.6 ± 1.4 T2 -0 ± 1.2 T3 -1 ± 1.4 C -1.2 ± 1.2	-	-	*Only descriptive* Bone structure of approximately two-thirds of samples was exclusively trabecular. Remodelling of woven bone into lamellar bone was the most common observation	-
Gholami 2012	GBR (T1) vs GBR (T2)	-	-	*Data per socket* T1 -1.1 ± 1	T1 27.4 ± 12.4 total bone; 20.6 ± 9.9 RGM T2 28.6 ± 12.5 total bone; 13.7 ± 8.1 RGM	-

				T2 -0.9 ± 0.6		
Hoang 2012[§]	Grafting (T1) vs grafting (T2)	T1 -0.1 ± 1.8 T2 0 ± 1.9	-	T1 -1.4 ± 1.5 T2 -1.3 ± 1.5	T1 48.8 VB; 8.2 RGM; 43.1 CT T2 52.7 VB; 5.4 RGM; 41.9 CT	-
Huh 2011[§]	Grafting (T1) vs grafting (T2)	T1 -0.1 ± 1 T2 -1.1 ± 1.4	-	-	-	-
Iasella 2003[i§]	GBR vs unassisted healing	T 1.3 ± 2 C -0.9 ± 1.6	T -0.1 ± 0.7 C -1 ± 0.8	T -1.2 ± 0.9 C -2.6 ± 2.3	T 28 ± 14 VB; 37± 18 non-vital; 26 ± 11 trabecular; 9 ± 6 amorphous C 54 ± 12 VB; - non-vital; 34 ± 12 trabecular; 12 ± 9 amorphous	*Changes in buccal gingival thickness* T -0.1 ± 0.5 C +0.4 ± 0.6
Jung 2013b[i]	Grafting (T1) vs sealing (T2) vs sealing (T3) vs unassisted healing	T1 -2 ± 2.4 T2 0 ± 1.2 T3 1.2 ± 2.9 C -0.5 ± 0.9	-	T1 -6.1 ± 2.5 T2 -1.2 ± 0.8 T3 -1.4 ± 1 C -3.3 ± 2	-	-
Karaca 2015	Sealing vs unassisted healing	T -0.012 ± 1.24 C -1.42 ± 1.5	-	-	-	-
Kim 2014[§]	GBR (T1) vs GBR (T2)	T1 -1.2 ± 0.8 T2 -1.5 ± 1.1	-	T1 -1.1 ± 1.3 T2 -1.2 ± 1.3	-	-
Lindhe 2014*	Sealing (T1) vs sealing (T2)	-	-	-	T1 39.9 ± 8.6 mineralized bone; 1.8 ± 2.5 bone marrow; 1.6 ± 1.8 osteoid; 32.4 ± 9.2 fibrous tissue T2 57.4 ± 12.4 mineralised bone; 7.1 ± 6.1 bone marrow; 7.3 ± 4.9 osteoid; 23.1 ± 16.3 fibrous tissue; 3.3 ± 1.7 vascular tissue	-
Mardinger 2012*	Sealing	-	-	-	40 ± 19 bone (13.7 to 74.8); 25.7 ± 13 (0.6 to 51) RGM; 34.3 ± 15 (13.8 to 71.9) CT	-
Meloni 2015	Sealing (T1) vs Sealing (T2)	T1 -1.6 ± 0.7 T2 -1.5 ± 0.6	-	T1 -0.5 ± 0.3 T2 -0.7 ± 0.3	-	-
Neiva 2008[§]	Grafting (T1) vs grafting (T2)	T1 0.2 ± 1.8 T2 -0.6 ± 1	-	T1 -1.3 ± 1 T2 -1.4 ± 1.1	T1 29.9 ± 8.5 VB; 65.3 ± 6.4 bone marrow and fibrous tissue; 6.3 RGM T2 36.5 ± 7.7 VB; 62.7 ± 7.4 bone marrow and fibrous tissue	-
Patel 2013[§]	GBR (T1) vs GBR (T2)	-	T1 -0.4 ± 1 T2 0.2 ± 0.7	T1 -1.1 ± 1 T2 -2.1 ± 1	*Only descriptive* Similar characteristics both groups. Newly formed bone mainly at apical part of biopsy. In coronal part, particles surrounded by dense connective tissue with no signs of inflammation. No active resorption of graft particles.	-
Perelman-Karmon 2012*	GBR (T1) vs grafting (T2)	-	-	-	T1 40.8 ± 10.6 total bone fraction T2 29.7 ± 7.2 total bone fraction	-
Pinho 2006	GBR (T1) vs GBR (T2)	-	-	T1 -1.4 ± 1 T2 -1.4 ± 2	-	-
Poulias 2013[§]	GBR (T1) vs GBR (T2)	T1 0.5 ± 2.9 T2 0.3 ± 2.6	T1 -0.5 ± 0.4 T2 -0.6 ± 0.4	T1 -1.6 ± 0.8 T2 -0.3 ± 0.9	T1 35 ± 16 VB; 21 ± 13 non-vital bone; 44 ± 9 trabecular space T2 40 ± 16 VB; 17 ± 11 non-vital bone; 43 ± 12 trabecular space	-
Serino 2003*	Grafting vs unassisted healing	-	-	-	*Only means provided* T 66.7 mineralized bone; RGM could not be identified C 43.67 mineralized bone	-
Vance 2004[§]	Grafting (T1) vs GBR (T2)	T1 -0.3 ± 0.7 T2 0.7 ± 1.2	T1 -0.2 ± 0.7 T2 -0.5 ± 0.5	T1 -0.5 ± 0.8 T2 -0.5 ± 0.8	T1 61 ± 9 VB; 3 ± 3 RGM; 32 ± 10 trabecular; 4 ± 4 amorphous T2 26 ± 20 VB; 16 ± 7 RGM; 54 ± 15 trabecular; 5 ± 6 amorphous	*Changes in soft tissue thickness* T1 Buccal +0.1 ± 0.6; Lingual -0.1 ± 0.7 T2 Buccal -0.2 ± 1.5; Lingual 0 ± 0.7
Wallace 2013*	GBR (T1) vs GBR (T2)	-	-	-	*Mean (range)* T1 41.8 (16 to 66) VB; 6.6 (0 to 29) RGM;: 51.6 (32 to 64) marrow/CT T2 32.5 (7 to 66) VB; 16.9 (0 to 29) RGM; 50.6 (34 to 65) marrow/CT	-
Wood 2012[§]	Grafting (T1) vs grafting (T2)	T1 -0.4 ± 1.1 T2 -0.6 ± 1.2	-	T1 -2.2 ± 1.6 T2 -2.1 ± 1.7	T1 38.4 ± 14.5 VB; 8.9 ± 12.8 RGM; 52.7 ± 8 CT T2 24.6 ± 13.7 VB; 25.4 ± 17 RGM; 49.9 ± 11.1 CT	-

Data provided as mean ± SD unless noted otherwise; patient is unit of analysis unless specified otherwise; dimensional changes provided in millimetres
*All studies included for Question 2; highlighted studies included for Question 1; [i] = selected for meta-analysis Question 1 [§] = selected for meta-analysis Question 2 * = included only for histologic data*
VB = vital bone CT = connective tissue RGM = residual graft material

e) Histological Characteristics of New Bone Formation

The histological characteristics of the new tissue, formed within the socket following ARP were described in 24 studies (Aimetti et al., 2009, Barone et al., 2013b, Beck and Mealey 2010, Borg and Mealey 2015, Calasans-Maia et al., 2014,Cook and Mealey 2013, Crespi et al., 2009a, Crespi et al., 2011a, 2011b, Eskow and Mealey 2014, Fiorellini et al., 2005, Gholami et al., 2012, Hoang and Mealey 2012, Iasella et al., 2003, Lindhe et al., 2014, Mardinger et al., 2012, Neiva et al., 2008, Mardas et al., 2010, Perelman-Karmon et al., 2012, Poulias et al., 2013, Serino et al., 2003, Vance et al., 2004, Wallace et al., 2013)(Wood and Mealey, 2012) (Wood and Mealey, 2012). Only a descriptive analysis was undertaken in this section, as extensive variation was present in the treatment protocols and biomaterials materials used as well as in the histologic methods applied to evaluate socket healing. Bone histological samples were reported upon by descriptive analysis, percentage tissue composition (bone / connective tissue / residual particles), mineralised bone content (Aimetti et al., Barone et al., 2013b and Gholami et al., 2012) and cellular bone composition (cellular / acellular / trabeculla). The included studies reported on the histological characteristics of the trephined core samples over a 10 week to nine-month period. The majority of the reports examined histological composition of the core samples at 3 months of healing.

GBR

Seventeen groups from ten studies (Barone et al., 2013b- two groups, Borg and Mealey 2015-two groups, Cook and Mealey 2013-two groups, Gholami et al., 2012-two groups, Iasella et al., 2003, Mardas et al., 2010-two groups, Perelman-Karmon et al., 2012, Poulias et al., 2013-two groups, Vance et al., 2004 and Wallace et al., 2013-two groups) report on histological composition of bone samples following GBR procedures. The results from these studies showed a high level of variation in the total bone percentage recorded with a range between 47.9 ± 9.1% to 24.67 ±15.92% reported. Four studies (Barone et al., 2013b, Borg and Mealey 2015-one group, Gholami et al., 2012 –two groups and Vance 2004) reported a total bone composition of less than 30%, five (Barone et al., 2013b-one group, Borg and Mealey 2015-one group, Cook and Mealey 2013-one group, Poulias et al., 2013-one group and Wallace et al., 2013-one group) found a 30-40% bone percentage and four (Cook and Mealey 2013-one group, Perelman-Karmon et al., 2012-one group, Poulias et al., 2013-one group and Wallace et al., 2013-one group) reporting over 40%. The use of a combined FDBA and DFDBA (Borg and Mealey 2015) or collagen / alloplast (Cook and Mealey 2013) graft, produced statistically more bone ($p<0.05$) when compared with a control using a single allograft or xenograft. The addition of denatured allograft material (Borg and Mealey 2015) significantly lowered the percentage of residual graft particle ($P=0.035$). The addition of a bone growth factor also increased the bone composition (Wallace et al., 2013). No qualitative differences were recorded between ceramic composite and DBBM (Mardas et al., 2010) or when different xenografts were tested (Barone et al., 2013b). The depth of the core sample

was found to statistically (P<0.001) influence the bone composition in one study (Perlman-Karmon 2012). Residual and / or encapsulated graft particles were found in five studies (Borg and Mealey 2015, Cook and Mealey 2013, Mardas et al., 2010, Vance et al., 2004 and Walace 2013), with the percentage of residual graft particles ranging from 3 to 16.9%.

Socket Grafting

Twenty four groups from fourteen studies(Aimetti et al., 2009, Beck and Mealey 2010-two groups, Calasans-Maia 2014-two groups, Crespi et al., 2009a-two groups, Crespi et al., 2011a-three groups, Crespi et al., 2011b, Eskow and Mealey 2014-two groups, Fiorellini et al., 2005-three groups, Hoang and Mealey 2012-two groups, Neiva et al., 2008-two groups, Perelman_Karmon 2012-one group, Serino et al., 2003, Vance et al., 2004 and (Wood and Mealey, 2012)-two groups) reported on histological composition following various socket grafting procedures. The average trabecular bone composition was recorded by Aimetti et al., (2009) to be 58.8% and by Fiorellini et al., (2005) 66.6 %. Eskow and Mealey (2014) reported on new bone formation (range 13-16.13%), Perelman-Karmon et al., (2012) reported on a total bone fraction (range 29.7-40.8%) and Serino et al., (2003) measured the average mineralised bone percentage (66.7%). The composition of vital bone formation recorded was highly variable, with the percentage recorded ranging from 19.3% (Beck et al., 2010) to 61% (Vance et al., 2004). Three studies (Calasans-Maia et al., 2014- one group, Neiva et al., 2008 and Vance et al., 2004) reported a vital bone composition of less than 30%, four studies (Calasans-Maia et al., 2014- one group, Crespi et al., 2011a-two groups, Crespi et al., 2011b, (Wood and Mealey, 2012)) reported a vital bone composition of 30-40%, and four studies (Beck and Mealey 2010-two groups, Crespi et al., 2009a-two groups, Hoang and Mealey 2012-two groups and Vance et al., 2004) reported a vital bone composition of more than 40%. No statistical difference was recorded in the vital bone composition when different alloplasts, allografts and xenografts were compared (Beck and Mealey 2010, Calasans-Maia et al., 2014, Crespi et al., 2011a, and Hoang and Mealey 2012). Eskow and Mealey (2014) did not observe a statistical difference between cortical or cancellous graft material, and Hoang and Mealey (2012) failed to observe a difference when using different sized particles of human demineralised bone matrix. A significant difference in the trabecular bone formation was found when human growth hormone or calcium sulphate was added to the graft material (Fiorellini et al., 2005, Crespi et al., 2009a, Neiva et al., 2008 and Vance et al., 2004). Demineralised freeze-dried allograft generated more vital bone formation when socket grafting using methylcellulose, calcium sulphate and bone allograph was compared against GBR using a bovine xenograft and collagen membrane (Vance et al., 2004). More vital bone was also recorded when socket grafting was undertaken with a demineralised rather than mineralised freeze-dried bone allograft ((Wood and Mealey, 2012)). Residual and or encapsulated graft particles were found in twelve studies (Beck and Mealey 2010, Calasans-Maia et al., 2014, Crespi et al., 2009a,2011a, 20011b, Eskow and Mealey 2014, Hoang and Mealey 2012, Neiva et al., 2008, Serino et al., 2003, Vance et al., 2004 and (Wood and Mealey, 2012)), with the percentage of residual graft

particles ranging from 0% with a polylactide sponge (Serino et al., 2003) to 36.6% with a corticocancellous xenogenic graft (Crespi et al., 2011a) to. No inflammatory response was reported within the histological graft specimens.

SS Techniques

Three groups from two studies (Lindhe et al., 2014-two groups and Mardinger et al., 2012) reported on bone composition following a SS procedure. Lindhe et al., (2014) examined the effect of SS with a collagen membrane or membrane / bovine xenograft combination. Mardinger et al., (2012) evaluated the additional benefit of using the reactive socket tissue as a seal overlying a bovine xenograft. Histological examination by Lindhe et al., (2014) reported 39.9 ±8.6% mineralised bone and 19.5 ±6.5% residual graft in the group combining xenograft with a collagen seal, and 57.4 ± 12.4% mineralised bone in the collagen seal alone group. Mardinger et al., (2012) reported 40 ±19% vital bone in the core samples. Three studies (Cook and Mealey 2013, Lindhe et al., 2014 and Mardas et al., 2010) reported fibrous encapsulation of graft particles, with four studies (Borg and Mealey 2015,Crespi et al., 2011b Lindhe et al., and Hoang and Mealey 2012) reporting new bone formation in direct contact with the graft particles. with inflammation recorded in the healed overlying gingival tissues.

f) Histological Characteristics of New Bone Formation

The depth of the core sample was found to positively influence the composition of new bone formation, with a larger percentage of new bone found in the apical section of the core (Aimetti 2009 and Perelman-Karmon et al., 2012). Three studies (Cook and Mealey 2013, Lindhe et al., 2014 and Patel Mardas et al., 20103) reported fibrous encapsulation of graft particles, with four studies (Borg and Mealey 2015,Crespi et al., 2011b Lindhe et al., and Hoang and Mealey 2012) reporting new bone formation in direct contact with the graft particles. No studies reported on signs of inflammation within the histological samples. Although inflammatory cells were a common finding in the core biopsies after ARP, loose graft particles and remnants of the membrane were not usually seen.

g) Post-operative Complications

The presence or absence of complications were reported in twenty nine studies (Aimetti et al., 2009, Barone 2013a and 2014, Beck and Mealey 2010, Borg and Mealey 2015, Calasans-Maia et al., 2014, Camargo et al., 2000, Cardaropoli et al., 2014, Cook and Mealey 2013, Coomes et al., 2014, Crespi et al., 2011a and 2011b, Eskow and Mealey 2014, Fernandes et al., 2011, Festa 2013, Fiorellini et al., 2005, Gholami et al., 2012, Hoang and Mealey 2012, Jung et al., 2013b, Karacas et al., 2015, Kim et al., 2014, Meloni et al., 2015, Mardas et al., 2010, Perelman-Karman 2012, Pinho et al., 2006, Poulias et al., 2013, Serino et al., 2003, Wallace et al., 2013 and (Wood and Mealey, 2012) (Table 23).

The most common findings were soft tissue inflammation and possible infection (Beck and Mealey 2010, Cook and Mealey 2013, Coomes et al., 2014, Fiorellini et al., 2005, Karacas et al., 2015, Mardas et al., 2010, Wallace et al., 2013 and (Wood and Mealey, 2012)). Loose graft particles or deficient socket fill at the ARP site was reported in three socket grafting groups (Beck and Mealey 2010- one group, Eskow and Mealey 2014, Hoang and Mealey 2012) and one GBR (Mardas et al., 2010) study. Patient discomfort was reported in four studies (Cardaropoli et al., 2014, Fiorellini 2005, Karacas et al., 2015 and Mardas et al., 2010). Membrane exposure was recorded in three GBR studies following surgical intervention (Cook and Mealey 2013, Mardas et al 2010 and Pinho 2006).

h) Patient-based Outcomes

No studies reported on patient preferences or any other patient-based outcomes following ARP preservations (Table 23).

***Table 23**. Study outcomes of included papers (II)*

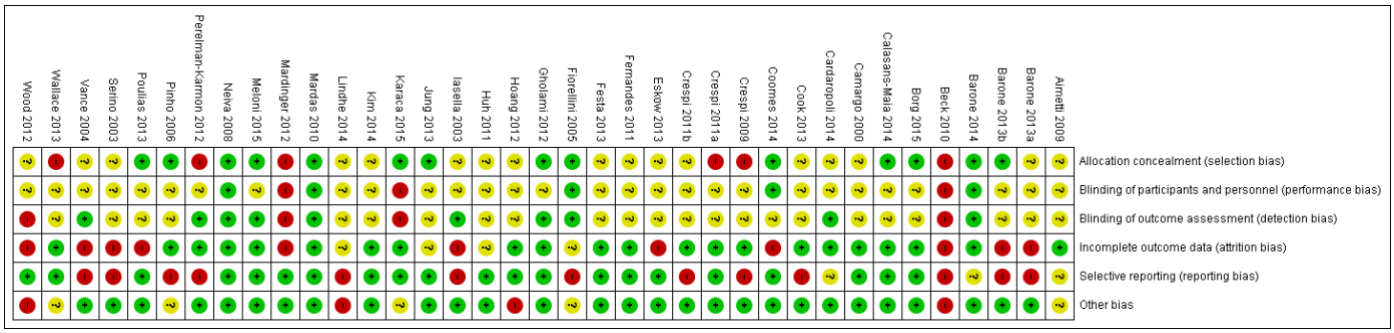
Reference	Complications
Aimetti 2009	None reported
Barone 2013a	None reported
Barone 2013b	-
Barone 2013c	None reported
Beck 2010	T1: post-operative infection (2 sites, ? patients); deficient fill of socket at 7-10d follow-up (3 patients) T2: post-operative infection (1 patient)
Borg 2015	None reported
Calasans-Maia 2014	None reported
Camargo 2000	None reported
Cardaropoli 2014	Discomfort and swelling were commonly reported in both groups
Cook 2013	T1: apparent postoperative infections at the treatment site that resolved within 1 week after switching antibiotic regimens (1 patient) T2: apparent postoperative infections at the treatment site that resolved within 1 week after switching antibiotic regimens (1 patient), patient reported removing the OP membrane during the initial 2 weeks of healing (1 patient)
Coomes 2014	Mild erythema and localized postoperative swelling 2 to 3 days after extraction (12% of patients)
Crespi 2009a	-
Crespi 2011a	None reported
Crespi 2011b	None reported
Eskow 2014	T1: 1 site lost graft particles from the socket during initial healing which was seen at 1-week postoperative
Fernandes 2011	None reported
Festa 2013	None reported
Fiorellini 2005	A total of 250 adverse events were reported for 78/80 patients. The most frequent reports were oral oedema (75%), mouth pain (68%) and oral erythema (46%). There were a greater number of cases of oral oedema and erythema in treatment groups compared to the no treatment group
Gholami 2012	None reported
Hoang 2012	T2: sequestering of some superficial pieces of bone graft material at the 1-week recall (2 patients)
Huh 2011	-
Iasella 2003	-
Jung 2013b	None reported
Karaca 2015	All patients experienced mild to moderate pain at donor site
Kim 2014	No severe adverse events reported.
Lindhe 2014	-
Mardinger 2012	-
Meloni 2015	None reported
Neiva 2008	-
Patel 2013	Few patients in both groups reported minor postoperative pain or discomfort, localized oedema and in some cases exfoliated graft particles were observed. All the patients presented with membrane exposure at the first postoperative week that, in most cases, became larger during the second week
Perelman-Karmon 2012	None reported
Pinho 2006	Exposure of membrane in 5 of the 10 treated subjects between the sixth and tenth week of the placements
Poulias 2013	None reported
Serino 2003	None reported
Vance 2004	-
Wallace 2013	None reported
Wood 2012	T1: 2 patients showed signs of potential infection at 1-week T2: 1 patient showed signs of potential infection at 1-week
All studies included for Question 2; highlighted studies included for Question 1	

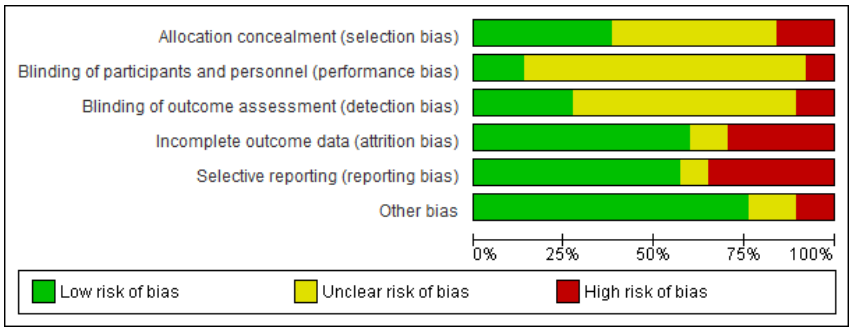
3.6 Quality assessment and risk of bias

The quality assessment of all the included studies for both focused questions are presented in figures 11a and 11b. Only two studies were assessed as having low risk (Neiva et al., 2008 and Mardas et al., 2010). Three other studies were assessed as having a low risk of bias in all but one domain (Barone et al., 2013c, Gholami et al., 2012 and Meloni et al., 2015), and three studies presented with a low risk of bias in four domains (Borg and Mealey 2015, Calasans-Maia et al., 2014 and Huh et al., 2011). All other studies were considered to have an unclear to high risk of bias.

Other sources of bias were the lowest risk category reported, when examining the papers. Uncertainty in the blinding of the participants and the outcome assessment, was the commonest finding. The highest risk of bias was associated with selective reporting.

Figure 11. *Quality assessment of the included papers: (Upper) Risk of Bias Graph. (Lower) Risk of Bias Summary. Please note that the risk of bias evaluation is based on the original publications only.*





13.7 Discussion

13.7.1 Objectives and main findings

Augmentation procedures have been proposed as a method to limit the adverse functional and volumetric tissue changes experienced during healing after a tooth extraction (Mardas et al., 2015, Tan et al., 2012, Vignoletti et al., 2012). They have been recorded as changing the structural and histological characteristics of the bone and gingival tissue (Block and Kent, 1990, Horváth et al., 2013, Lindhe et al., 2013, Vignoletti et al., 2014), possibly promoting the establishment of an idealised functional, biologic and aesthetic foundation, before implant supported or conventional prostheses are provided (Mardas et al., 2015).

The adoption of ARP has been proposed as a method to significantly improve the aesthetic outcome of single-tooth implants in the anterior maxillary. Particularly as they may help to retain sufficient bone at dental implant sites to allow fixture placement (Mardas et al., 2015), reduce the risk of subsequent bone loss (Horváth et al., 2013), positively influenced the design of the prosthetic tooth (Pagni et al., 2012) and improve the emergence profile of the restoration (Belser et al., 2004) simplifying access for oral hygiene activities. Anticipated soft tissue effects have included an increase in the gingival papilla height and expansion of the fixed keratinised tissue height and width.

This review found that significantly less vertical alveolar bone height resorption occurred when ARP was compared to unassisted socket healing. These finding are in agreement with the results published by Horváth et al., (2013), and Vignoletti et al., (2011) and Morjaria et al., (2014). Although a mean reduction in alveolar bone width resorption of 1.20 mm was recorded, this finding was not statistically significant when compared to unassisted socket healing. This observation is at odds with that reported by Vignoletti et al., (2011), but this difference may be accounted for by the heterogeneity of the included data, the methodological structure of the review and the limited number of included trials reporting on this finding. When this study was compared with the systematic review performed by Vignoletti et al., (2012), it was found that seven of the twelve identified papers, did not perform statistical analysis and that three of the remaining five papers were excluded from this study due to insufficient patient numbers, duplicate reporting and incompatible study design.

Histology

Histologically, an increase in bone content was found in the ARP group in comparison to the control group. This was also reported in the systematic review by De Risi et al., (2013) and in certain groups in the systematic review by Horváth et al., (2013). ARP studies however, reported a higher level of complications and an increased frequency of oedema, facial pain and erythema (Fiorellini et al., 2005 and Karacas et al., 2015). No studies reported on other variables associated with the patient experience.

Although various surgical techniques and materials have been used for ARP, no material or type of ARP intervention can be claimed to yield superior results to another (Horváth et al., 2013, Mardas et al., 2015, De Risi et al., 2013). Previous systematic reviews concluded that the use of barriers for GBR appeared to be more effective in limiting post-extraction dimensional changes of the alveolar ridge (Horváth et al., 2013, Vignoletti et al., 2012; Avila-Ortiz et al., 2014). Although direct statistical comparison was not possible, a greater vertical bone dimensional change was recorded following GBR when compared with the dimensional findings for socket grafting. The amount of horizontal bone dimensional change was noted to be greater with socket grafting than that reported for GBR procedures.

Keratinised Tissue

Keratinised tissue measurements were not commonly reported following ARP procedures. This is surprising since the conservancy of the fixed keratinised tissues might affect long-term peri-implant health and decrease the risk for biologic complications (Tan et al., 2012), if an implant supported restoration is considered. GBR techniques appeared to result in an increase in the keratinised tissue width when no attempt at primary closure was undertaken. No change in the soft tissue width was reported when socket grafting was used. The thickness of the gingival tissues was slightly reduced with GBR procedures (Iasella et al., 2003 and Vance et al 2004, with a small gain noted when using a combination of collagen/particulate socket graft (Vance et al 2004).

The use of GBR or socket grafting techniques in this systematic review seemed to produce a similar range of bone composition (vital and trabecular bone) in histological samples. The effect of using different GBR, socket grafting materials and particle size on new bone formation was inconclusive, as no statistical advantage was reported in the reviewed RCTs. Demineralised freeze-dried bone was reported as having a statistical influence on the creation of the new vital bone fraction in socket grafting techniques. More vital bone was reported in the apical area of core samples, when compared with coronal sections.

The depth of the core sample was found to influence the bone composition (Aimetti 2009 and Perelman-Karmon et al., 2012). Although the presence of residual graft particle has been recorded as interfering or disrupting the process of bone healing, only three of the twenty-four studies (Cook and Mealey 2013, Lindhe et al., 2014 and Mardas et al., 201o) reported on fibrous encapsulation of the graft particles, with no studies reporting on inflammation within the core samples.

Patient Based Outcomes

The incidence of complications reported within the ARP studies was low. Loose graft particle or deficient socket fill was the commonest adverse event in socket graft procedures (Beck and Mealey 2010, Eskow and Mealey 2014 and Hoang and Mealey 2012), with exposure of the membrane reported in three out of ten included GBR studies. An exposure of the graft particle was associated with the presence of fibrous encapsulation within the histological specimen (Cook and Mealey 2013).

3.7.2 Strength and weakness of the systematic review

As in the previous systematic review, two focus questions were formulated to try to ensure that all available relevant information outlining ARP outcomes was included in the study. The first focused question limited inclusion to RCTs, CCTs and prospective cohort studies, with a control group of unassisted socket healing in order to identify comparative site dimensional and qualitative tissue effects following ARP procedures. This was based on the fact that the clinical merit of applying ARP is based on the assumption that they will have an additional positive effect on tissue conservancy and bone characteristics over unassisted healing and will validate use of the procedure. For the second focused question, controlled studies without a control group and large prospective case series were also included, to ensure that that as much of the available published data was used to estimate pooled tissue changes according to three types of interventions for ARP.

Although a comprehensive search strategy including five databases, extensive hand and cross-reference search and no language restriction were applied, it is possible that some grey literature may not have been included as only published studies were selected. In order to obtain as much data as possible from published studies, the authors of 9 studies selected for full-text screening, were contacted via email to request further information relating to the dimensional and histological changes following ARP. Some authors failed to respond within the requested time period, therefore, it is possible that further information exists which could be used to complement the data set used in this review.

The total number of subjects and selected studies for *focused questions 1 and 2* could be considered sufficient for the assessment of effect size differences between ARP and unassisted socket healing and to calculate mean bone and soft tissue dimensional changes following GBR and socket grafting ARP procedures. Limited data was available however to evaluate the influence of SS techniques on site dimensional changes, histological characteristics and patient outcome factors and as a result the findings in this section of the analysis should be interpreted with caution. Finally, the sample sizes of all the selected clinical trials were relatively small, with many not including a sample size calculation. This small number of participants may reduce the statistical power of the studies.

3.7.3 Confounding Factors

Socket Wall

As the majority of studies in this systematic review had at least three walls of the socket intact, with more than 50% of the fourth wall remaining intact, the impact of socket wall integrity on the ARP outcome is relatively unknown. The tooth extraction sites were recorded as being heterogeneous, minimising the effect of the position of the extracted teeth on the outcomes.

Measurements

The method used to measure the alveolar bone dimensions varied in several studies. Twenty-two of the twenty-seven included studies used direct measurements from static casts, in preference to CBCT radiographic images. As static cast measurements can be influenced by the impression technique and soft tissue changes, difference in the effect of the intervention may have occurred. The possible variation that this may have caused in the recorded measurements was not considered in this review.

Patient-based outcomes

As a significant number of publications did not report on this finding, then there may be a higher risk of under-reporting.

Anti-microbial Use

Antibiotics were commonly prescribed as an adjunct to ARP, with extensive variation in prescription pattern, dose and length of use. Antibiotic prophylaxis in alveolar and implant surgical procedure has been shown to have a small statistic effect on healing and outcome Esposito et al., (2008). The impact of this variable was not considered as a component of this review.

3.8 Conclusion

A reduction in horizontal alveolar bone dimensional change was found when ARP was compared to unassisted socket healing, but the difference between techniques was not found to be statistically significant. ARP resulted in a significant reduction in the vertical bone dimensional change when compared to unassisted socket healing. No evidence was identified to clearly indicate the superiority of either GBR, socket filler or SS ARP techniques on bone dimensional preservation or keratinized tissue

dimensions. This lack of superiority indicated that currently, it is not known if a specific biomaterial or treatment protocol is advantageous.

When examining the histological bone composition, there was insufficient evidence available to show a difference in the amount of vital bone formation following GBR or socket grafting techniques, with inflammation of the gingival tissue commonly observed at the grafted sites following ARP.

The majority of the studies evaluating ARP procedures presented with high or unclear risk of bias. Clinical recommendations derived from this study should be interpreted with caution.

Chapter 4

Alveolar Ridge Preservation with Guided Bone Regeneration or a Socket Seal Technique. A Randomised, Single-Blind Controlled Clinical Trial

Material and Methods

4.1 Introduction (Clinical study description)

As healing of the extraction socket has been demonstrated to lead to extensive vertical and horizontal tissue resorption (Demircan and Demircan, 2015), with the risks associated with dimensional change particularly evident in the anterior maxilla (Araujo et al., 2015), ARP techniques have been developed to promote favourable healing and preservation of the bone and soft tissue structures (Iocca et al., 2017, Avila-Ortiz et al., 2019, Canullo et al., 2021).

Although there is recognition that GBR and SS ARP techniques (Horváth et al., 2013, Darby et al., 2008, Wang et al., 2004) can be used to better preserve ridge dimensions in comparison to unassisted socket healing, differences have been recorded in the contour of the healed alveolar bone, the requirement for additional bone augmentation at implant placement and the surgical and longer-term complications attributed to each procedure.

This study was designed to compare the radiographic bone changes, following alveolar ridge preservation (ARP) using Guided bone regeneration (GBR), a socket seal (SS) technique, or unassisted socket healing (Control).

- *Null Hypotheses*

There is no difference in the alveolar bone dimensions and healing characteristics when unassisted healing is compared with ARP at a tooth extraction site.

This Randomised Controlled Trial (RCT) was designed as a single-centre, prospective, single blind clinical trial, that examine the characteristics of bone and gingival healing following ARP using a SS or GBR ARP technique at 4 months healing. Linear dimensional changes and cross-sectional area transformation was assessed using direct clinical measurements, CBCT imaging and optical scans. The RCT also set out to reviewed patient socket healing characteristics, pain experience, implant and aesthetic outcomes and histological healing characteristic. Unassisted healing acted as the control, with the configuration and dimensional changes examined, prior to Type-3 implant placement).

Due to the extensive area of investigation, the RCT was split into five investigative areas. The domains included:

The **Primary Outcome** measure was the change in the radiographic vertical dimensions of the buccal and palatal alveolar crest, following ARP using a SS or GBR technique when compared with unassisted healing.

The **Secondary Outcome** measures included:

- Radiographic Dimensions and patient outcomes

The radiographic measurements included: i) The change in horizontal radiographic socket dimensions, ii) The radiographic thickness of the buccal bone plate at a position 5mm and 10mm below a reference stent, iii) Radiographic cross-sectional socket and alveolar process area measurements, iv) Healing complications at the extraction socket, v) Pain scores during initial healing, vi) Intra-oral clinical parameters including full mouth bleeding scores (FMBS) and plaque scores (FMPS).

- Alveolar Ridge Dimensional and Gingival Tissue Morphological Changes

The tissue measures included: i) The buccal and palatal horizontal profilometric (contour) change, following ARP using a SS or GBR technique and unassisted healing. Dimensional changes were recorded at the gingival cervical margin and at 5mm depth, following 4 months healing. ii) The change in the buccal and palatal, alveolar ridge contour height, iii) The horizontal and vertical extent of the buccal and palatal mucosal tissue remodelling, iv) The width and thickness of the keratinised tissue.

- Histological Examination of an ARP and Unassisted Healing Extraction Socket

Comparison of the histological composition of a healed tooth extraction site, following ARP using a GBR or SS techniques at 4 months healing. Core samples were examined using Back Scatter Electron-Scanning Electron Microscopy (BSE-SEM) and X-ray Micro-Tomography (XMT) imaging.

- *Implant survival and Success*

Implant and patient outcome measures included: i) implant placement feasibility, ii) The requirement for additional bone augmentation at implant placement (4 months), iii) Implant success and survival rates,

4.2 Ethical approval and case administration

The study was conducted in full accordance with the ethical principles of the Declaration of Helsinki (version, 2008) and ISO 14155, and was independently reviewed and approved by the Ministry of Defence Research Ethics Committee (MODREC). All procedures were performed between 2015 and 2019. CONSORT guidelines for reporting clinical trials were followed (http//: www.consort-

statement.org). Assessment of patient suitability for implant placement was determine according to the guidelines stipulated in Surgeon Generals Policy (JSP 950-2-23-1, SG-PSD, Part 2 - Annex D)

4.2.1 Patient information and informed consent

Before enrolment, patients were informed of the clinical investigations being examined within the study. The risks and benefits of enrolment were detailed, with a comprehensive discussion undertaken of the immediate and long-term risks associated with implant treatment and ARP. The patient was then given two information sheets summarising the discussed information (Annex A- Participant Information Sheet 1 and 2), with 24-hrs allocated to consider the proposal, before the patient was asked to consent to participation in the study (Annex B).

The study consent form was then signed by an independent witness and the investigator. A separate consent was undertaken detailing the risks associated with extraction of the tooth and at the time of implant placement (Annex B). These declarations of consent were undertaken to re-iterate to the patient the unique risks associated with ARP and implant treatment.

4.2.2 Case report forms (CRF)

The investigator was given responsibility for the accuracy and data entry into a specifically designed CRF form. Separate CRF forms (Annex C) were constructed for each of the study visits, according to a pre-planned timeline. These CRF forms were used to record the clinical data associated with the primary and secondary outcome variables. All entries were written in black or blue ink, with all deletions, additions or changes initialled and dated. The lot numbers and product information from the bone graft materials and the implant components were also stored on the CRF form. All patient information was stored in a locked location, with this information only available for review by other members of the investigating panel.

4.2.3 Records/Data retention

All clinical radiographs were stored in accordance with Defence Primary Health Care and Defence Dental Service policy. Originals of the radiographs, CRF, casts or other items and originals of the study records were stored in a secured storage location. A digital back up of recorded digital x-ray images was saved on an external hard drive and positioned in a fire-poof safe at the end of every session. Original X-ray and CBCT images were stored on the patient's dental record on the Defence Medical Information Computer Program (DIMCP). The patient was given full disclosure of the medical devices utilised during their care, at the completion of treatment.

All study documentation (CRFs, investigators files, patient radiographs and photographs) will be kept

at the study site after the study is completed for at least 10 years, to allow the investigator to answer any queries associated with the study. These records will then be archived and maintained indefinitely, according to Defence Medical archive procedures.

4.2.4 Protocol Amendments

Once the first patient has entered the study, protocol changes shall be kept to a minimum. Only those changes that are deemed essential to the successful completion of the protocol will be entertained. If changes to the protocol are proposed, they shall be discussed with the clinical monitor in a timely manner and the MODREC committee notified. Additional Ethical Committee approval will be required for any change in the investigation plan that may affect the scientific soundness of the investigation or the right, safety, or welfare of the patient.

4.5 Reporting Adverse Risks

All patients were monitored for adverse tissue or medical reactions / complications at all visits after the surgery (Annex D). Monitoring of adverse events (AEs) would be conducted throughout the study in accordance with ISO 14155 (2011). New adverse events, including serious adverse events (SAEs), would be recorded on the case report forms (CRFs) at all visits. SAEs will be immediately reported to the Research Project Safety Committee Chairman and to the Principal Investigator and monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or inter-current illness(es). Adverse events would be reported to the investigator on the Adverse Event / Complication form within 5 working days (Annex D).

4.3 Study Population

The four investigative areas described in this thesis used the same study population and surgical protocol. An outline of the study population and the surgical GBR and SS ARP techniques is outlined below.

4.3.1 Inclusion criteria

Military patients attending a specialist secondary care referral practice, who present with a terminal prognosis maxillary single rooted incisor, canine or premolar tooth, requiring extraction and prosthetic replacement using an implant supported restoration. Extraction could have been precipitated due to trauma, periodontitis, endodontic complication or unrestorable caries. Fifty-two (52) patients were originally screened for eligibility, with 43 patients enrolled in the study.

The eligibility criteria included male or female military patients, aged 18 years to 55 years of age, who were systemically fit and well. Patients with a previous diagnosis of periodontitis were required to have successfully completed a course of periodontal treatment before enrolment, with disease stability demonstrated over a 6 month period. A thick gingival biotype and a FMPS of below 15% and a FMBS below 10% was also required at study baseline. The gingival biotype was assessed using a probe as described by Jepsen et al. (2018). It was assumed that the periodontal probe (Hu-Friedy, Chicago, IL, USA) would be visible when the biotype is thin (gingival tissue ≤1 mm) and not visible when thick (gingival tissue >1 mm). The accepted characteristics for the extraction socket included, a buccal alveolus, with less than 3mm or 25 % of the buccal contour lost. The integrity of the buccal socket wall was assessed clinically and using the CBCT radiograph following tooth extraction. Adequate mesio-distal space was required for implant placement.

4.3.2 Exclusion Criteria

The exclusion criteria for the study included smokers, pregnant or lactating females and patients with uncontrol diabetes, active systemic illness, infection or patient who had undergone recent surgical treatment. Patients prescribed phenytoin, dihydropyridine, calcium antagonists, cyclosporine and anticoagulant therapy, or with a history of a severe bruxing / clenching habit, alcoholism, chronic drug abuse and psychological disorders were also excluded.

Local exclusion factors included the presence of a clinically symptomatic periapical radiolucency, acute abscesses, chronic sinus tracts and a residual periodontal pocket depth of > 5mm, at the completion of the pre-treatment periodontal therapy.

4.3.3 Patient Enrolment

On the patient's first visit, the medical history, dental status, full mouth PPD, FMBS, REC and MFPS scores were recorded. All clinical measurements were documented by a single, previously calibrated examiner, using a manual UNC-15 periodontal probe with light probing force (20 gr/N). Periodontal indices were recorded at six sites: mesio-buccal, mid-buccal, disto-buccal, mesio- palatal, mid-palatal, and disto- palatal around the dentition.

An upper and lower alginate impression (Imprint., 3M, UK) was taken to record the baseline morphology of the extraction site. The working cast was fabricated using Type IV stone (GC Corp., Tokyo, Japan).

4.4 Study timeline

After enrolment, the patients were seen at the following visits:

a. Enrolment visit.

b. ***Baseline evaluation*****:** Extraction and augmentation of extraction socket according to randomization visit. CBCT examination undertaken following tooth extraction.

c. Post-operative control visits at 1 to 2 weeks and 8 weeks.

d. ***Clinical, radiographic and histological outcomes recorded****:* 16 weeks evaluation visit (± 7 days) with review CBCT examination. Implant placement, with trephined bone sample collected. A record of the need for additional GBR augmentation was recorded.

e. Second stage surgery at 28 weeks.

f. Post-operative control visit.

g. Implant impression at 36 weeks

h. Restoration and loading of implant and evaluation of ARP site

i. 6 months post loading review and patient follow-up visit.

j. *PhD termination*: 12 months post loading review and follow-up visit.

4.4.1 Timeline for Data Collection

The timeline for the collection of the primary and secondary outcome measure is detailed in Table 24.

4.5 Minimally traumatic tooth extraction

One hour prior to tooth extraction, patients were prescribed a course of 500mg of Amoxicillin, which was continued three times daily for the following 5-day post-operative period. In the case of a reported allergy to penicillin, 500 mg of erythromycin was prescribed four times daily as an alternative. A 0.2% chlorhexidine rinse was administered before treatment, with Paracetamol 500mg prescribed for post-operative pain control.

A circumferentially surgical incision was then undertaken within the confines of the gingival sulcus, separating the periodontal attachment apparatus from the root of the tooth. Extraction of the tooth was facilitated using a luxator periotome and extraction forceps (Mardas et al., 2010), with care taken to preserve the integrity of the socket bone and gingival tissue boundary. Curettage of the socket was performed to remove residual granulation tissue. If the bony wall was noted to be severely damaged or lost during the extraction procedure, the patient was excluded.

The patient was then enrolled sequentially into the study, with the operative clinician provided with an envelope from an independent administrator, detailing the treatment allocation of either SS, GBR or Control. The envelope sequence was created from a master randomisation list that was held at the Defence Centre for Rehabilitative Dentistry, with the operator blinded to the allocation prior to treatment. All subsequent CBCT and clinical assessments were undertaken with the assessor blinded to the ARP treatment allocation.

Table 24 *– Timeline for RCT Investigative Studies Data Collection*

	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9	VISIT 10	VISIT 11	Visit 12
	Enrolment Visit	Extraction of tooth	Suture removal	Post-op Visit	CBCT Implant Placement	Post Op Review	Second stage surgery	Post Op review	Implant Impression	Restoration of Implant	6 Month Follow-up	12 Month Follow up
	0	Baseline (+1)	2 Weeks	8 Weeks	16 Weeks	18 Weeks	24-28 Weeks	30 Weeks	36 Weeks	40 Weeks	66 Weeks	92 Weeks
Primary and Secondary Outcomes												
Vertical Clinical measurements		x			x		x		x			
Optical Surface Analysis					x					x	x	
Keratinised Tissue measurement		x		x	x		x		x	x	x	x
Gingival Margin Thickness					x							
CBCT measurements		x			x							
Implant prosthetic placement					x							
Implant graft requirement					x							
Histology Sample					x							
Pain evaluation		x	x	x	x	x	x	x	x	x	x	x
Implant success criteria							x	x	x	x	x	x
Implant survival						x	x	x	x	x	x	x
Intraoral photographs		x	x	x	x	x	x	x	x	x	x	x
Wound healing assessment			x	x		x		x				
Pink Esthetic Score (PES)										x	x	x
White Esthetic score (WES)										x	x	x
Papilla Fill Index										x	x	x
Time Taken		x			x		x					
Adverse event / SAE		x	x	x	x	x	x	x	x	x	x	x
Concomitant Drug Therapy		x	x	x	x	x	x	x	x	x	x	x
Accessory Records												
Full mouth plaque score	x	x		x	x		x		x	x	x	x
PPD, REC, CAL, BOP		x		x	x		x		x	x	x	x

4.6 GBR and SS ARP techniques

In the GBR group, the extraction socket was filled with a xenograft bone substitute (DBBM) (Bio-Oss®; Geistlich Biomaterials, Wollhusen, Switzerland) up to the pre-extraction level of the buccal and lingual/palatal alveolus bone plate. A localised tissue flap was then raised circumpherentially around the socket rim, to allow placement of a collagen barrier membrane (Bio-Gide®, Geistlich Biomaterials, Wollhusen, Switzerland) 2 -3mm onto the adjacent alveolar bone surface. The extension of the flap in the mesial and distal interproximal areas was designed to avoided complete detachment of the adjacent gingival papilla. The localised mucosal flap was then replaced without major coronal advancement and

secured in place with Ethylon® 6(0) (Johnson & Johnson Medical N.V., Belgium) cross-mattress sutures. The sutures were placed in both the mesio-distal and bucco-palatal direction, to allow maximum stabilisation of the exposed membrane (*Fig. 12*).

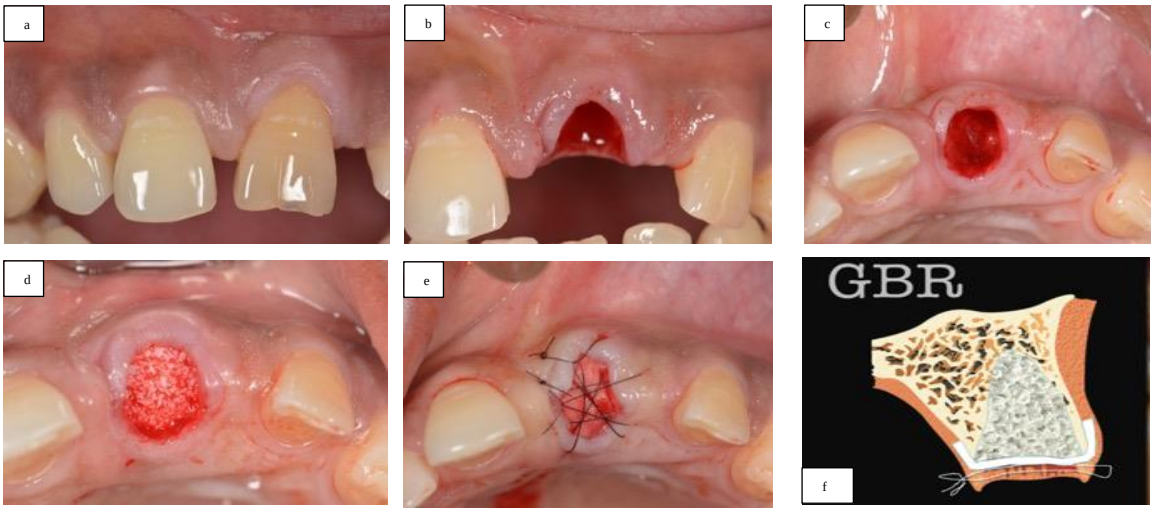


Figure 12. *Photographs demonstrating Surgical Protocol for ARP using GBR technique (a) The incisor in position 21 prior to extraction. (b) Atraumatic tooth extraction following incision of the gingival tissue. (c) De-epithelialization of the gingival tissue collar and localised flap raised. (d) Socket filled with a xenograft bone substitute. (e) The collagen membrane was sutured in place to seal the socket aperture. (f) Graphical representation of ARP using GBR.*

Figure 13 *Photographs demonstrating Surgical Protocol for ARP using SS technique (a) The incisor in position 11 prior to extraction. (b) Atraumatic tooth extraction with de-epithelialization of the gingival tissue collar. (c) Socket filled with a xenograft bone substitute. (d) A collagen matrix placed over the xenograft bone substitute (e) Mucograft® matrix sutures in place to seal the socket aperture. (f) Graphical representation of ARP using SS.*

In the SS group, de-epithelialization of the gingival tissue collar was undertaken using a high-speed, round, coarse diamond bur, with the extraction socket filled with the same xenograft bone substitute (DBBM) and the coronal aspect of the grafted socket covered with a cut to shape collagen matrix (Mucograft®) according to the manufacturer guidelines. The Mucograft® matrix was held in place, by suturing the top layer to the gingival tissue using single interrupted Ethylon® 6-0 sutures (*Fig. 13*).

In the control group, haemostasis and clot stabilisation was achieved by the direct application of pressure to the extraction site for five minutes using a rolled sterile gauze pack, soaked in saline (*Fig. 14*

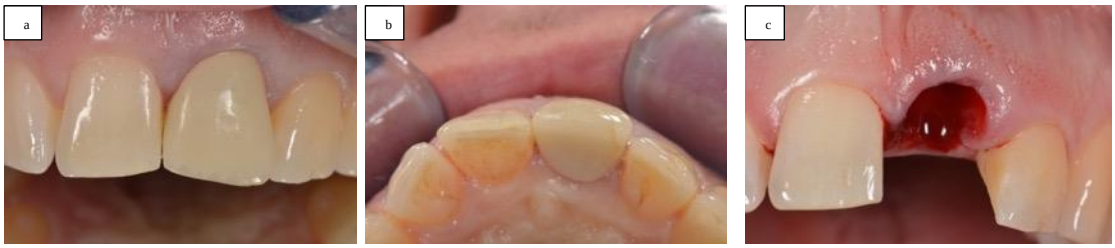


Figure 14. *Control patient demonstrating unassisted socket healing protocol. (a) and (b) Pictures of the incisor in position 21 prior to extraction. (c) Socket left to form primary clot, prior to application of sterile pack.*

4.7 Post-operative instructions

The patients were instructed not to wear the immediate tooth replacement for 24hrs and to avoid strenuous physical activities for 72hrs, to prevent disruption or displacement of the primary clot. After 24hrs, a 0.2% chlorhexidine-di-gluconate mouthwash was initiated, three time per day, with a modified brushing and oral care programme resumed in the upper maxilla at 72hrs and respected for a further 11 days. Suture removal was scheduled for 14 days, with a dental hygienist visit providing tooth debridement and oral hygiene reinforcement at 2 weeks and again at 8 weeks.

Radiographic Alveolar Bone Dimensional Changes and Patient Outcomes

Material And Methods

5.1 Manufacture of a radiographic reference stent

Prior to tooth extraction, an upper and lower alginate impression (Imprint., 3M, UK) was taken to record the baseline morphology of the extraction site. The working cast was fabricated using Type IV stone and annotated as the pre-surgical models. A thermoplastic matrix was manufactured extending three teeth either side of the extraction site. The tooth planned for extraction was sectioned from the cast, with the model trimmed to the buccal and palatal gingival contour. The thermoplastic material was then adjusted to the outlined gingival contour and filled internally with a barium sulphate radiopaque filler. This stent was designed to be used as a stable radiographic reference, to enable the measurement and comparison of dimensional changes immediately after extraction and following 4 months of healing. Reference points were marked with a depressed vertical grove in the mesial (M), middle (MID) and distal (D) areas of the buccal and palatal aspects of the stent, to ensure consistence in the vertical orientation and measurement position (*Fig. 15*). If the crown of the tooth to be extracted was missing or damage, a diagnostic wax-up of the tooth was undertaken in the residual space, using the current gingival margin to determine the emergence profile. This wax-up was duplicated and the radiographic matrix manufacture on this cast, to aid future comparative measurements.

The patients were asked to wear the stent during CBCT imaging, with radiographic images taken immediately after tooth extraction (primary) and at 4 months healing (secondary), prior to implant placement. The CBCT images were captured using a Carestream 9300 x-ray unit, with the patient's inter-arch position stabilised with a local customised index. An image field size of 5cm by 5 cm, at a voxel size of 200 μm, scanning time 12 second, tube voltage of 60-90 KV and a frequency 140 KHz was selected.

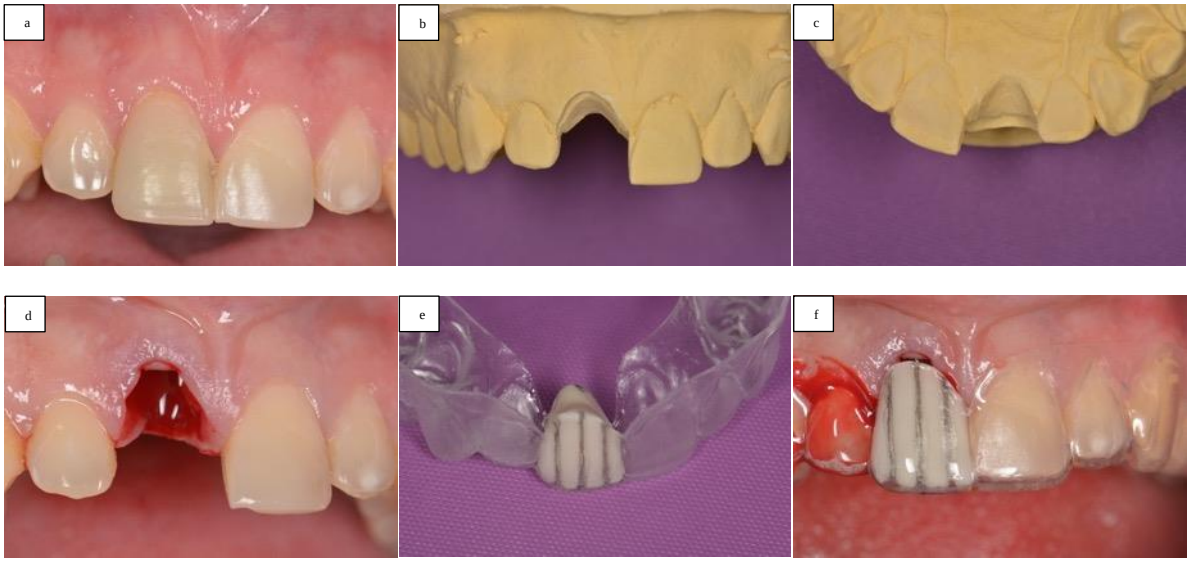
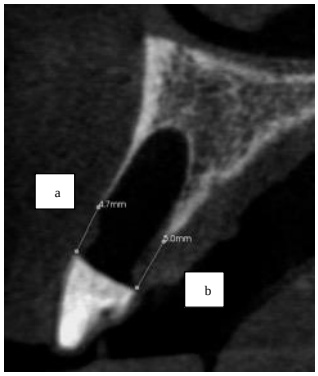


Figure 15 *- Manufacture of radiographic measurement stent at extraction site. (a) The incisor in position 11 prior to extraction. (b) 11 sectioned from the cast and buccal aspect trimmed to gingival margin position (c) Palatal aspect trimmed to gingival margin contour. (d) Extraction socket immediately following tooth removal. (e) Radiographic reference stent constructed to marked gingival contour. (f) Gingival margin positional change, immediately following tooth removal.*

5.2 Vertical alveolar ridge height

Post extraction and 4 month CBCT DICOM (Digital Imaging and Communications in Medicine) data files, were imported into the OnDemand3D software suite (Version 1.0.10.5385- Cybermed, USA). The Profile Measurement Tool was selected to measure the vertical distance between the crest of the alveolar ridge and the base of the radiographic stent. The Profile Measurement Tool assesses the variation in bone/tissue grey-scale pixel density along a demarcated line, to aid in the detection of the edge of an anatomical surface, when partly mineralised bone was under investigation.

The vertical alveolar ridge height (ARH) was determined by measuring the distance from the base of the radiographic stent to the uppermost point of the alveolar bone crest in the M, Mid and D positions, on both the buccal (BARH) and palatal (PARH) aspect of the extraction socket. The primary outcome measure was assessed as the change in the radiographic vertical BARH and PARH measurement in the three test groups, following 4 months healing (*Fig. 16*).



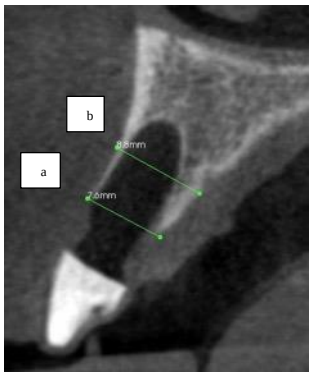
a) Buccal alveolar ridge height (BARH): The distance from the buccal alveolar bone crest to the base of the reference measurement stent.

b) Palatal alveolar crest ridge height (PARH): The distance from the palatal alveolar bone crest to the base of the reference measurement stent.

Figure 16. *CBCT radiographic measurement of the MID BARH and PARH. a) Buccal alveolar ridge height (BARH): The distance from the buccal alveolar bone crest to the base of the reference measurement stent. b) Palatal alveolar crest ridge height (PARH): The distance from the palatal alveolar bone crest to the base of the reference measurement stent.*

5.3 Radiographic and patient-based outcomes

Horizontal Alveolar Ridge Width: The horizontal Alveolar Ridge Width (ARW) was measured using the Profile Measurement Tool at the Mesial, Mid and Distal positions, at a distance of 5mm (the Cervical ARW - CARW) and 10mm (the apical ARW- AARW), from the radiographic stent (*Fig. 17*). The dimensional change in the CARW and AARW measurements were assessed following 4 months healing.



a) Coronal alveolar ridge width (CARW): The external width of the alveolar ridge at a distance 5mm from the radiographic stent.

b) Apical alveolar ridge width (AARW): The external width of the alveolar ridge at a distance of 10 mm from the index.

Figure 17. *CBCT radiographic measurement of the alveolar height and ridge width. a) Coronal alveolar ridge width (CARW): The external width of the alveolar ridge at a distance 5mm from the radiographic stent. b) Apical alveolar ridge width (AARW): The external width of the alveolar ridge at a distance of 10 mm from the index.*

5.4 Buccal socket wall thickness

The thickness of buccal socket thickness was recorded at 5mm and 10mm below the radiographic stent using the profile measurement tool (*Fig. 18*).

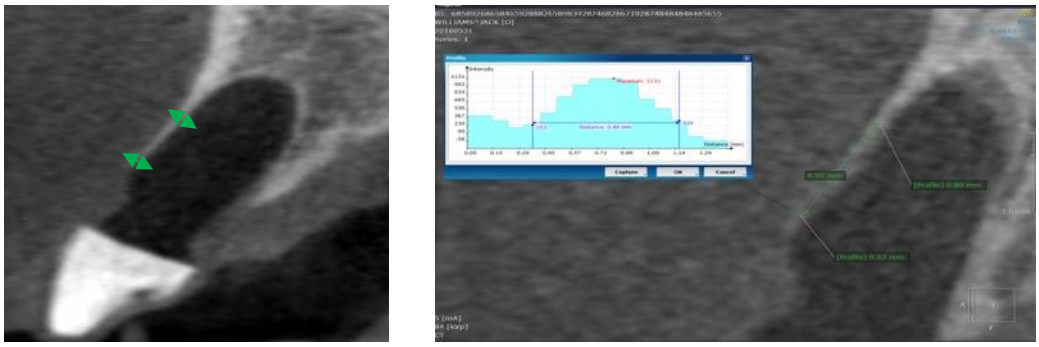


Figure 18. *CBCT Images demonstrating the 5mm and 10mm buccal socket measurement positions (a) and the grey scale histogram (b) produced by the Profile Measurement Tool, which was used to assist in the measurement of the buccal socket wall thickness.*

5.5 Cross-sectional socket and alveolus area measurements

The OnDemand3D software allows for the superimposition of two CBCT images, imported as separate DICOM files, through a registration and merging function. Alignment of the CBCT images was achieved through a three-staged process. Initially, the primary and secondary images were fused using an auto registration tool, in an attempt to alignment the axial, sagittal and coronal planes. The fused images were then checked for accuracy of registration on a monitor. Errors in alignment were corrected using a mutual information algorithm, with the procedure repeated to obtain the best fit.

Once the registration alignment was established, the secondary DICOM data set was reconfigured using the resliced tool, to conform to the axial, sagittal and coronal configuration of the primary image. Merger of both the primary and secondary images was undertaken using two different colour masks, to allow for differentiation and accurate visual assessment of the alveolar bone changes over the 4 months healing period (*Fig. 19*)

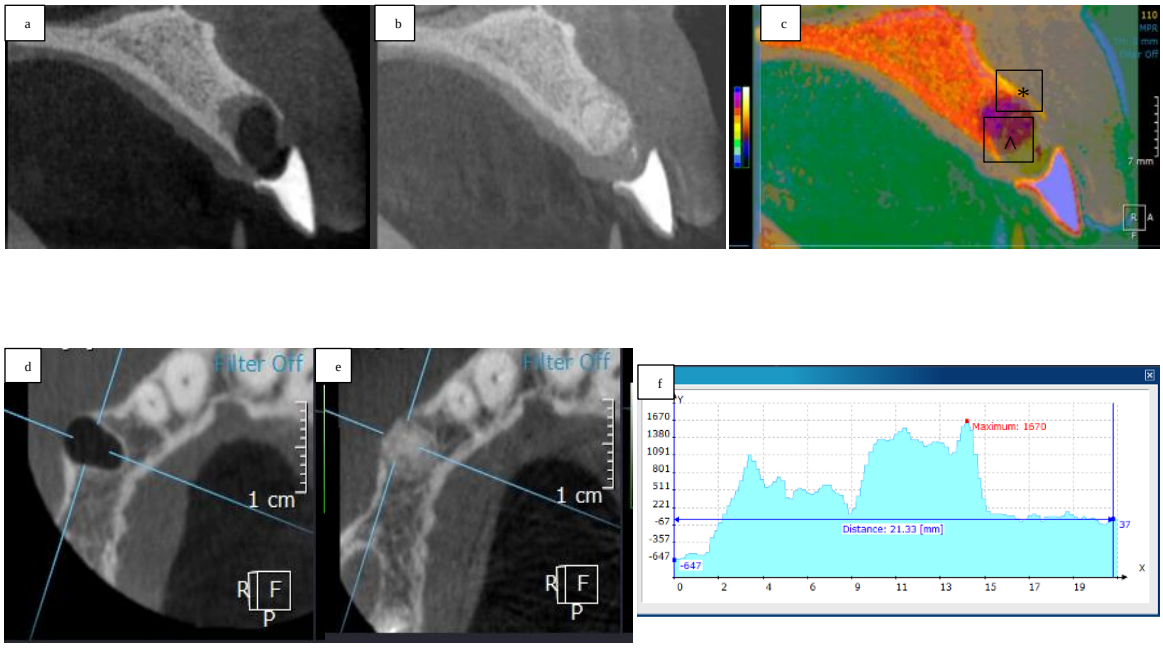


Figure 19. *Superimposed CBCT Images demonstrating Alveolar bone change following 4 months healing. (a) primary CBCT image taken after tooth extraction. (b) Secondary CBCT image taken at 4 months healing. (c) Merged primary and secondary CBCT images, visualised using different colour masks. (d) Primary Axial Plane. (e) Secondary Axial Plane. (f) Graph from profile measurement tool, which was used to assess the dimensions of the alveolar ridge along the measurement axis. (*) orange colour represents original bone profile. (^) purple overlay outlines the residual morphology of the alveolar ridge when the secondary CBCT image was taken (4 months).*

The initial CBCT image was used to outline the internal surface of the extraction socket and the extent of the original alveolar process supporting the root of the tooth. The apical aspect of the socket was used as the base of the alveolar process, with the base determined as the bisecting plane, drawn parallel to the bucco-palatal coronal socket orientation. The socket (SA) and alveolar process (APA) cross-sectional area (mm^2) was then calculated. The merged image was then examined, using the primary image socket and alveolar process outline as a reference. The level of bone infill (mm^2) in the extraction socket and the change in the cross-sectional area of the outlined alveolar process was then calculated (*Fig. 20*).

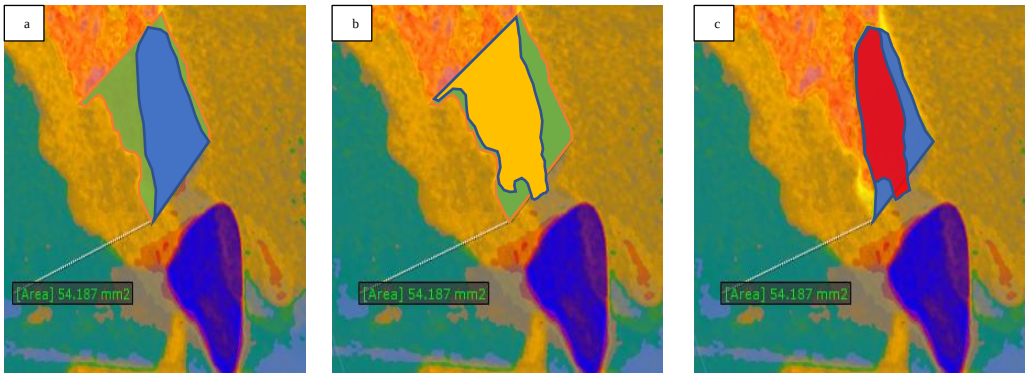


Figure 20. *Measurement of socket and alveolar process cross-sectional area (mm^2. (a) Primary socket (blue) and alveolar process areas (green). b) Primary alveolar process outline (green) and secondary healed outline (yellow). (c) Primary socket outline (blue), secondary healed outline (red).*

5.6 Post-operative surgical complications

An evaluation of the extraction site was undertaken at the 2 week control visit. The presence of patient side effects or complaints were recorded as being dichotomously present or absent in a case report form. The complications logged included suppuration at graft site, the presence of swelling, persistent pain in the grafted area swelling, expulsion / sequestration of grafted material, tissue reaction to graft material, resorption and remodelling of the graft, colour and tissue morphological changes and clefting of the gingival tissue. Recession of the gingival tissue, sensitivity from the adjacent dentition, chronic pain, local infection, loss of and dehiscence of the membrane was also recorded.

5.7 Pain intensity scores (Visual Analogue Scale)

The patient's pain intensity score was recorded using a visual analogue scale (VAS) at 2 weeks and at 8 weeks healing (*Fig. 22*). Patients were asked to mark on the analogue scale, the point that they felt represented their perceived perception of their current pain state. The VAS score was measured in millimetres from the left-hand end of the line to the point that the patient marked.

The patient's pain experience was classified according to the following threshold values: no pain (0–4 mm), mild pain (5-44 mm), moderate pain (45–74 mm), and severe pain (75–100 mm)(Jensen et al., 2003).

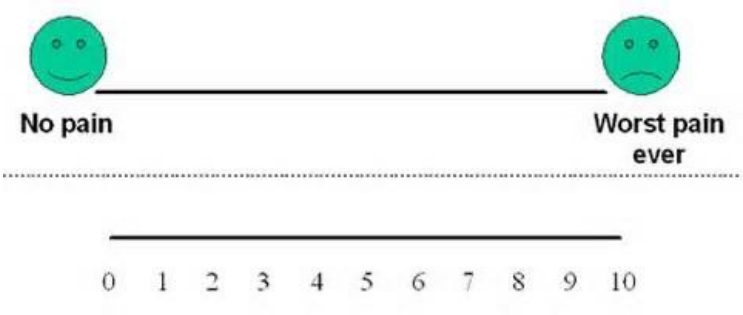


Figure 21. *VAS used for pain assessment with recording scale detailed below.*

5.8 Power calculation

Assuming a CBCT radiographic vertical change of -0.5mm in the unassisted healing control group, with a standard deviation of 0.9mm (Jung et al., 2013b) and an effect size of 0.8mm, then a three grouped study would require a sample size of 14 to produce an 80% power at an alpha level of 5%.

5.9 Statistical analysis and randomisation

All data was entered in a computer database, proofed for entry errors and loaded in the SPSS statistical software package (v.22). Tissue dimensions at tooth extraction and at 4 months healing, were recorded as a mean ± standard deviation for the three test groups.

Data normality was assessed by the Shapiro Wilk test and Levene's test of Variance. If the data was normally distributed the differences between the groups was assessed using parametric methods. If the assumptions were not fulfilled, non-parametric tests were used instead. Significance was set at $p < 0.05$.

Parametric Tests:

i) Independent samples t-tests for differences in means between groups.

ii) One-way fixed effect ANOVA. If a significant difference was observed between the groups from the one-way ANOVA, a Tukey's honestly significant difference post hoc analysis was performed to check which specific groups differed.

Non-Parametric tests:

i) Independent Wilcoxon rank sum test between groups.

ii) Kruskal–Wallis non-parametric one-way analysis of variance. If a significant difference was observed between the groups a post hoc analysis was performed using Dunn's procedure. A Bonferroni correction for multiple comparisons was used and adjusted *p*-values were presented.

An intra-class correlation coefficient was used to measure the level of intra rater reliability CBCT radiographic measurements (10 sets), repeated over a 10-day interval.

Chapter 6

Radiographic Alveolar Bone Dimensional Changes and Patient Outcomes Following ARP

Results and Discussion

6.1 Study population

The study population consisted of 43 individuals, 42 male and 1 female. One male patient was lost from the study, due to military deployment. The average age of enrolled patients was 32 years, with an age range of 27 – 53 years. Fourteen patients were allocated in each of the SS, GBR and Control groups. FMPS and FMBS scores were recorded at less than 10%, for all patients during treatment.

6.2 Tooth extraction position

All patients underwent extraction of a single rooted tooth in the upper anterior maxilla (15- 25 position), with thirty-six central incisor teeth, one canine and five premolar teeth removed. The five premolars, were observed to have an oval root morphology and fused roots at the apex, conforming to the inclusion criteria.

6.3 Outcome measures

Vertical Alveolar Ridge Height Dimension (BARH and PARH)

After 4 months of healing, analysis of the CBCT images revealed that the GBR, SS and Control groups had all experienced vertical alveolar ridge height dimensional change.

A decrease in the Mid-BARH and Mid-PARH dimensions was found when using the GBR and the SS techniques, demonstrating vertical augmentation of the alveolar crest height. GBR resulted in a small increase in the Mid-BARH of 0.07mm (SD 0.83) and a Mid-PARH of 0.86mm (SD 1.37), with the SS technique producing an increase in the Mid-BARH and Mid-PAH of 0.65mm (SD 1.1) and 0.65mm (SD 1.42) respectively. In the Control group, an increase in the Mid-BARH (0.52mm SD 0.8) and Mid-PARH (0.43mm SD 0.83) dimensions was found, indicating resorption of both the buccal and palatal alveolar bone crests (Table 25).

The GBR ARP technique reported more height gain in the Mesial and Distal measurement sites (6%). Palatally, all three groups demonstrated the greatest dimensional change in the Mid-PARH position.

When comparing the SS and Control test groups using a one-way ANOVA calculation, a statistically significant difference in Mid-BARH ($p = 0.007$) was found between SS and the Control and Mid-PARH ($p= 0.02$) between the GBR and the Control. The intra-class correlation co-efficient demonstrated a measurement reliability of 0.91 with a CI (0.86 to 0.95).

25 Alveolar Ridge Dimensions at Tooth Extraction and Dimensional Changes at 4-months Healing (mm)

Test Protocol		M-BARH	Mid-BARH	D-BARH	M-PARH	Mid-PARH	D-PARH	M-CARW	Mid-CARW	D-CARW	M-AARW	Mid-AARW	D-AARW
GBR	Mean	3.49	3.31	3.42	3.95	3.90	3.62	7.74	8.23	8.01	8.16	8.47	8.16
	SD	0.68	0.50	0.84	0.93	0.83	1.16	1.11	1.09	1.08	1.00	1.10	1.13
SS	Mean	3.55	3.64	3.51	3.76	4.04	3.79	8.35	8.83	8.66	8.53	8.41	8.92
	SD	0.88	0.86	0.75	1.00	1.11	0.90	1.10	1.15	1.12	1.28	2.43	1.10
Control	Mean	3.90	3.94	3.74	3.87	4.05	4.04	8.37	9.00	8.47	8.15	9.10	8.45
	SD	0.78	0.66	0.74	0.87	0.68	0.79	1.41	1.19	1.05	2.01	1.22	2.22
Dimension Change GBR 4-month	Mean	-0.24	-0.07	-0.27	-0.50	-0.86	-0.33	-1.73	-2.17	-1.89	-0.71	-0.96	-0.77
	SD	0.90	0.83	0.87	1.13	1.37	1.52	0.88	0.84	0.64	1.08	0.34	0.61
Dimension Change - SS 4-months	Mean	-0.27	-0.65	-0.11	-0.02	-0.65	-0.08	-3.03	-2.36	-2.91	-0.80	-0.86	-0.76
	SD	1.35	1.10	0.99	1.61	1.42	1.21	2.25	2.76	1.99	0.72	1.48	0.64
Dimension Change Control 4-months	Mean	0.59	0.52	0.52	0.39	0.43	0.33	-1.85	-2.30	-1.57	-1.22	-0.82	-0.71
	SD	1.03	0.80	0.84	1.26	0.83	0.75	2.48	1.11	2.43	1.42	0.76	0.47
One way ANOVA p-Value		0.09	0.007	0.07	0.263	0.02	0.362	0.2	0.96	0.165	0.46	0.938	0.955
F Test		2.574	5.6	2.49	1.384	4.23	1.045	1.679	0.038	1.894	0.791	0.06	0.045
Tukey HSD			SS Vs. Control P=0.005			GBR Vs. Control P=0.03							
Legend: BARH, buccal alveolar ridge height; PARH, palatal alveolar ridge height; CARW, cervical alveolar ridge width; AARW, apical alveolar ridge width; M, mesial; Mid, middle and D, distal.													

Horizontal Coronal and Apical Alveolar Ridge Width Dimensions (CARW and AARW)

Measurement for the horizontal width dimension changes are detailed in Table 25. At 4 months healing, the GBR group recorded a Mid-CARW reduction of -2.17mm (SD 0.84), with the SS group demonstrated the greatest Mid-CARW change of (-2.36mm SD 2.76). The Control was found to have a dimensional change of -2.30mm (SD 1.11).

These figures represent an individual Mid-socket CARW mean change of 26.4% for GBR, 26.7% when using the SS technique and 27.5% with unassisted healing. The SS technique reported a greater CARW reduction in the Mesial and Distal positions, when compared to the Mid-socket region, with this observation reversed in the GBR and Control groups.

The Mid-socket AARW reduction was similar for the GBR, SS and Control groups (-0.96mm (SD 0.34) for GBR, -0.86mm (SD 1.48) for SS, and -0.82mm (SD 0.76) for Control). These measurements equated to a mean AARW reduction of 10%, with only negligible differences in the ARRW found, when the Mid and Mesial and Distal socket dimensions were compared.

The ANOVA analysis revealed no statistical difference in the CARW and AARW dimensions changes at 4 months healing between all groups.

Buccal Alveolar Plate (Socket) Thickness

A mean Mid-Buccal alveolar socket thickness of 1.02 mm (SD 0.32) was recorded at the coronal aspect of the extraction socket for the enrolled patients, with a thickness of 1.04mm (SD 0.29) measured at 5mm and 1.02mm (SD 0.27) at 10mm. No evidence of buccal socket dehiscence or fenestration was noted in the CBCT images, with no statistic differences found, when comparing the buccal socket wall thickness in the GBR, SS, and Control groups.

At 4 months healing, only 2 patients in all three test groups, demonstrated evidence of retention of an aspect of the original buccal socket contour in the coronal 4-mm. These patients had a socket wall thickness of 1.9 and 2.4mm. All other patients demonstrated loss of the buccal alveolar bone plate.

Socket Area (SA) and Alveolar Process Cross-sectional Area (APA)

The Mid SA and APA was 51.34 mm^2 (SD 13.09) and 94.45 mm^2 (SD 26.6) in the GBR group, 58.86mm^2 (SD 12.32) and 110.50 mm^2 (SD 33.61) with SS, and 54.28 mm^2 (SD 14.8) and 102.37 mm^2 (SD 30.75) in the Control.

At 4 months healing, the GBR, SS, and Control groups all demonstrated a reduction in the mid-SA measurement. The mid-SA was reduced by 4% (-2.27mm^2 SD 11.89) in the GBR group, 1% (-0.88mm^2 SD 15.48) when using SS and 13% (-6.93MM^2 SD 8.22) in the Control. The GBR group demonstrated an increase in the SA in the mesial-SA (0.22mm^2 SD 7.88) and distal-SA (0.02 mm^2 SD 8.29) reference positions. The Control group demonstrated the greatest SA reduction at 4 months healing in the Mesial, Mid and Distal positions.

A reduction in the APA was again found in GBR, SS, and Control groups at 4 months healing. An 8% (-7.36mm^2 SD 10.45) reduction was observed in the Mid-APA when using GBR, with a 6% (-7mm^2 SD 18.97) reduction for SS group and a 11% (-11.32mm^2 SD 10.92) reduction in the Control. The Control group demonstrated greater APA loss in the mesial (16%) and distal (12%) positions, when compared to the mid-socket area (Table 26).

A Kruskal-Wallis One-way ANOVA analysis, with post hoc Bonferroni calculation, revealed a reveal a statistical difference in the Mid-SA between the GBR and Control test groups (p=0.01), at 4 months healing.

Table 26*. SA and APA at Tooth Extraction, and Area Changes at 4-Month Healing (mm^2)*

ARP Procedure		M-SA	Mid-SA	D-SA	M-APA	Mid-APA	D-APA
GBR	Mean	44.62	51.34	45.23	86.26	94.45	85.28
	SD	9.95	13.09	12.75	26.77	26.60	28.28
SS	Mean	53.31	58.86	57.35	101.43	110.50	108.72
	SD	12.15	12.32	13.14	28.86	33.61	30.56
Control	Mean	48.49	54.28	48.24	91.01	102.37	100.58
	SD	15.99	14.80	13.51	29.87	30.75	26.45
Area Change GBR	Mean	0.22	-2.27	0.02	-6.50	-7.36	-8.72
	SD	7.88	11.89	8.29	12.50	10.45	11.82
Area Change SS	Mean	2.45	-0.88	-3.36	-1.61	-7.00	-10.24
	SD	17.91	15.48	14.47	22.87	18.97	15.51
Area Change - Control	Mean	-7.80	-6.93	-4.00	-14.76	-11.32	-12.14
	SD	5.71	8.22	7.60	6.39	10.92	6.85
Kruskal–Wallis		0.32	0.05	0.19	0.067	0.83	0.786
H Test		2.26	5.4	3.31	6.28	0.389	0.482
Bonferroni Correction			GBR Vs. Control P=0.01				
Legend: SA, socket area; APA, alveolar process area; M, mesial; Mid, middle and D, distal.							

6.4 Post-operative surgical complications

Post-operative complications were regularly reported when using the GBR and SS ARP techniques (Table 27). Sloughing and localised breakdown of the collagen membrane was observed in 28% (4) of GBR patients, with loss of the membrane integrity predominantly recorded in the proximal areas. Graft sequestration was noted in 21% (3) of these cases. Inflammation was reported in 49% (7) of the GBR group, resulting in a localised mucosal colour change in 42% (6) of patients, during the initial stages of healing. These colour changes had resolved at the 8 weeks review.

Partial breakdown of the collagen matrix occurred prior to suture removal in 43% (6) of SS cases, with complete loss of the seal observed in 7% (1) patients. Loss of graft particles was reported in all of these cases. Inflammation 21% (3) and colour change 28% (4) was less frequently observed when using SS ARP and was again resolved at 8 weeks.

Table 27 *- Complications Associated with SS and GBR ARP and Tooth Extraction at 2 weeks*

ARP Procedure	Suppuration	Inflammation / swelling	Persistent pain	Expulsion or sequestration	Tissue reaction	Resorption of the graft	Colour changes	Clefting of the gingival tissue	Recession	Sensitivity	Chronic pain	Local or systemic	Loss of the membrane	Dehiscence
GBR		7		3			6		3	1				4
SS		3	1	7			4		4	2		1	1	6
Control		2		1			4	1	8	3				

One patient experienced a dry socket in the Control group, with delayed healing, pain and localised infection recorded in this case. Recession of the gingival margin was noted in 56% (8) of patients and was the most common outcome. The recession was found to be associated with a higher level of tooth sensitivity, with 21% (3) of patient recording this complication. Initial colour changes were also seen in 28% (4) patients (*Fig. 23*)

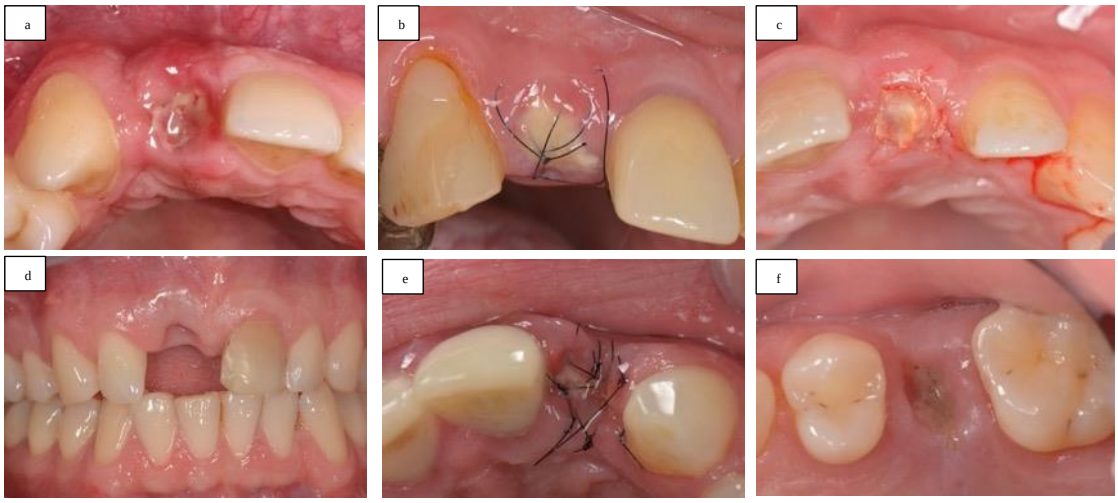


Figure 22 - *Pictures of socket healing at 2 weeks demonstrating local Complications. (a) Colour change with the GBR group. (b) Dehiscence of the membrane with SS. (c) Dehiscence of the membrane with GBR. (d) Tissue recession with Control. (e) Sequestration of graft with SS. (f) Partial loss of the membrane with SS.*

6.5 Visual analogue pain scores

At two weeks healing, four patients recorded a moderate level of residual pain (45-74mm), with two of these cases associated with more complex surgical tooth removal and one related to the presence of localised infection. No singular ARP technique or Control was found to be associated with increased pain scores for the patient. The SS ARP technique was linked with a slightly higher level of residual discomfort at suture removal (2 weeks). The GBR patients experienced no pain at 8 weeks, with the SS

and Control recording mild pain, but at the lower limit of this grading (Table 28). No statistical difference was recorded between the VAS pain scores for the SS, GBR and control groups.

***Table 28**. VAS Recorded Following Tooth Extraction And ARP*

ARP procedure	VAS score at Suture Removal	Patient Observations	VAS score at 8 weeks review
GBR	2.3 SD 1.37	One patient above 6	0.4 SD 0.3
SS	2.6 SD 1.67	Two patients above 6	0.5 SD 0.4
Control	2.21 SD 1.47	One patient above 6	0.56 SD 0.3
One way ANOVA p-Value	P=0.62		P=0.71
F Test	1.58		1.47
Tukey HSD			
Legend: VAS, visual analogue score (pain)			

6.6 Discussion

Healing at an extraction site is characterised by re-organisation, proliferation and maturation of the oral tissues, resulting in dimensional changes to the alveolar bone and gingival tissues (Avila Ortiz et al., 2019 and 2020). The amount of horizontal and vertical alveolar dimensional change is directly interlinked, as vertical crestal resorption can occur as a direct result of damage to the extraction socket, or due to a complex pattern of osteoclastic remodelling activity on either the inner and outer socket wall (Araujo and Lindhe, 2005), leading to both vertical and horizontal dimensional changes. This RCT established that GBR and SS ARP techniques, were effective in maintaining the vertical radiographic ARH, creating a more clinically favourable condition prior to implant placement.

6.6.1 Vertical dimension

Both GBR and SS ARP techniques, resulted in a vertical gain in the Mid BARH and Mid PARH dimensions when compared with the vertical loss in the Control group. Whilst the increase in the GBR group was small, vertical gain in the GBR and SS groups was at a level, that could be considered as clinically relevant. However, a statistically significant difference was only found in the SS and the GBR test groups in the Mid BARH (P =0.007) and Mid PARH (p=0.002) areas. Whilst the SS technique recorded a greater mean BARH and PARH gain than GBR, there was a higher level of variance in the measurements, potentially alluding to the potential for more complications with this technique. This variation may be due to the SS ARP technique allowing for a degree of over-extension of the bone graft above the coronal boundaries of the extraction socket, but this over extension being affected by a greater level of graft dehiscence during healing. This dehiscence risk affecting the predictability of the healed

outcome. Whilst the GBR technique is restricted in its ability to enhance the vertical alveolar crestal contour, as it requires the barrier membrane to be extended onto the peripheral bone surface, the superior occlusive properties of the barrier during the early healing period may allow for more predictable bone formation (Calciolari et al., 2018b).

Recent systematic reviews by Avila Ortiz et al., (2019) and Troiano et al., (2018) have supported the outcomes of this RCT, indicating ARP procedures effectively reduced the level of vertical alveolar ridge high contour change by between 1.65mm to 1.72mm, when compared to unassisted healing Control. A similar levels of vertical alveolar ridge height conservancy was reported when using the GBR technique (Barone et al., 2008, Cardaropoli and Cardaropoli, 2008, Crespi et al., 2009a, Jung et al., 2013b) and SS (Jung et al.,, 2013b) ARP's techniques. When using a SS procedure, Coomes et al., (2014) and Neiva et al., (2008) described a smaller level of alveolar ridge height preservation, with an overall reduction in vertical dimension. The reason that this RCT may have reported a moderate vertical height gain, in both the SS and GBR groups, may be attributed to the described advantages of the grafting protocol, the atraumatic extraction technique utilised (Thoma et al., 2019) and the flat or scalloped thick phenotype (Avila Ortiz et al., 2019; Thoma et al., 2019) required for patient inclusion.

Vertical BARH and PARH dimensional changes were found to be more extensive in the buccal and palatal mid-socket region, when compared to the proximal areas of both the ARP test and the Control groups. Excluding the grafting limitations already discussed, the difference in the morphometric dimensions of these results, correspond with the outcome measurements of the systematic review undertaken by Tan et al., (2012), which reported a weighted mean Mid-BARH reduction of 1.24 mm, at 3 to 7 months healing. Tan et al., (2012) also recorded a reduced alveolar ridge heigh loss proximally, with only a 0.8mm to 0.84 mm height loss in patients with unassisted healing. It was suggested that the different rates of proximal and mid-buccal bone remodelling, could be attributed to the blood supply from the interdental and periodontal ligament space of neighbouring teeth (Al-Hezaimi et al., 2011), with the additional vasculature contributing to the stabilisation of the proximal bone and a reduce risk of bone resorption.

6.6.2 Horizontal dimensions

This study reported a horizontal Mid-socket width reduction of -2.3mm (SD 1.11) or 25.5% in the Control group, which is slightly less that the outcomes (2.6mm to 4.6mm or 3.87mm SD 0.82) reported in the systematic reviews undertaken by Ten Heggeler et al. (2011) and Van der Weijden et al. (2009). The difference was attributed to the inclusion of multiple rooted teeth, with the 2.3mm (SD 1.1) CARW reduction found in this study, considered representative of the dimensional change for single rooted teeth in the maxillary dentition.

Comparison of the SS, GBR and Control Mid-CARW and AARW measurements, indicated a similar level of horizontal socket width reduction in all groups, at 4 month healing. This observation conforms to the findings of the meta-analysis undertaken in this thesis's systematic review, which indicated that whilst ARP may offer a clinically relevant reduction in alveolar width changes during socket healing, reducing the need for subsequent bone augmentation at implant placement, the magnitude of the reduction in horizontal alveolar dimensional change is variable (Avila-Ortiz et al., 2019). Whilst other studies have reported great conservancy of width dimensions, following ARP with a GBR (Aimetti et al., 2009, Barone et al., 2008, Barone et al., 2013b, Jung et al., 2013a) or SS (Meloni et al., 2015, Jung et al., 2013c) techniques, the high level of heterogeneity in the published data may account for the observed statistical differences.

Another difference may be attributed to the reference position used to measure the horizontal socket width. The socket width measurement are often taken at a more coronal positions (3mm), as this region has been found to suffer more extensive dimensional change (Araujo et al., 2015). This study recorded the horizontal socket width at 5mm and 10mm below the radiographic reference stent, as a more superficial position was not found to be associated with repeated retention of the buccal and palatal alveolar bone socket walls.

The minimally traumatic tooth extraction technique used in this study (Araujo and Lindhe, 2009, Sculean et al., 2019) and the restricting of enrolled patients, to those with a moderate to thick biotype (Cook et al., 2011), Thoma et al., 2019 and Chappuis et al., 2017), may also have influenced the level of horizontal socket remodelling experienced. An additional factor is the bias associated with the predominately male population group. Gender differences in alveolar bone dimensions have been chronicled by Lee et al (2019) and El Nahass et al., (2019), with the CBCT buccal socket thickness measurements (1.04 mm at 5mm and 1.02 mm at 10mm), higher than the population average reported by Tsigarida et al., (2020). As baseline buccal bone thickness has been demonstrated as being a predictor for buccal bone resorption (Araújo et al., 2015, Araujo and Lindhe, 2005, Tomasi et al., 2010), higher CBCT dimensions could potentially lead to reduced horizontal socket dimensional change.

This RCT population had a low power (P=0.255) to detect a 1mm horizontal size reduction of the CARW and AARW measurements for the SS and GBR test groups. These results suggest that a larger population size is required to demonstrate a statistical difference between ARP and control groups when examining the width changes in the alveolar ridge.

6.6.3 Area measurements

The SA and ARA cross-sectional changes are representative of the extent of socket alveolus bone resorption, bone regeneration and the amount of residual graft matrix visible on the radiograph. The

measurements described the healing pattern at the extraction socket and provide insight into whether additional bone grafting would be needed at implant placement.

Both the GBR and SS techniques reported a small loss of Mid-SA (1% and 4%) and Mid -APA (6% and 8 %) area, when compared to the area changes of 13% and 11% observed in the Control. GBR demonstrating a statistical difference to the Control in the Mid-SA area. A similar level of SA reduction (3%) was reported by Araujo et al., (2014), but this same study also indicated a higher ARA reduction of 25%. The observed difference may be as a result of variations in the selected outline of the alveolar ridge, differences in extraction techniques and the patient biotype characteristics outlined previously. The importance and effect of using different alveolar ARA boundaries can be appreciated by comparing the mean 102.49 mm^2 (SD 13.48) ARA reduction observed in this study, with the 99.1 ± 30.1$mm^{2.}$ ARP reduction found by Misawa (2016), who used a similar outline for analysis of the anterior maxillary alveolar ridge.

Whilst the SS group appeared to record a lower SA reduction, a higher level of horizontal SA dimensional change occurred with this technique, requiring greater vertical SA augmentation, to offset the buccal tissue resorption. Although GBR was observed to suffer a slightly higher level of SA change, when compared to SS, it was observed to have suffered a lower level of buccal tissue resorption and only vertical bone augmentation on the palatal aspect.

The ARA changes reflected the characteristics of the SA bone augmentation and healing pattern, recording only a small area of coronal palatal bone resorption, with the majority of the alveolar bone loss recorded in the crestal 4mm of the buccal socket wall for the SS, GBR and Control groups. This localised area of bone morphological change confirms the findings by Araújo and Lindhe (2005), Araujo (2015) and Tomasi et al 2010. Whilst it was anticipated that the need to raise a small flap to facilitate membrane placement for GBR might be associated with a higher level of bone resorption, it was observed that that the SS procedure suffered a greater level of buccal bone loss. This difference in resorption rates may be attributed to the GBR membrane offering greater protection to the grafted matrix in the bundle bone area, with improved bone healing characteristics (Retzepi and Donos, 2010).

6.6.4 Pain and complications

This study indicated that patient's experienced only mild pain following tooth extraction, with no difference noted in the patient's perceived pain experience during the initial 2 weeks of healing following ARP with either a GBR or SS technique. This low level of pain experience has been reported in several RCT's (Barone et al., 2013a, Camargo et al., 2000, Festa et al., 2013, and Jung et al., 2013b) and documented in the systematic review undertaken by Atieh et al. (2021).

Pain, oedema, and erythema were the most common surgical complications reported in both GBR and SS ARP test groups and the Control, with the frequency of these complications slightly higher when

using GBR (Cook and Mealey 2013, Mardas et al., 2010 and Pinho 2006) and SS (Fiorellini et al., 2005 and Karacas et al., 2015) procedures. Temporary colour change and membrane exposure with sequestra of the bone graft matrix was observed in both SS and GBR procedures and was attributed to the additional surgical trauma and the loss of a suture. When dehiscence of the collagen membrane and collagen matrix was reported, the loss of the membrane integrity was observed to be very localised and only caused limited graft sequestration. At 8 weeks healing, no observed differences were seen in the SS, GBR and Control groups.

6.6.5 New developments in study methodology

Alveolar Bone Measurements

This study used an innovative combination of optical scans, superimposed CBCT radiographs and overlayed mesh images to undertake comparative analysis of dimensional changes following two different ARP techniques and unassisted healing. Whilst the use of superimposed or fused images (Fickl et al., 2008a) has been documented, the accuracy of recorded measurements is influenced by the quality of the CBCT scans and their ability to display anatomical features. The image display is affected by the field of view, tube voltage and amperage, partial volume averaging, the presence of noise or artefacts on the image (Molen, 2010), soft tissue factors, voxel size and spatial resolution (Patcas et al., 2012, Molen, 2010).

The accuracy of measurement recorded by CT and CBCT machines has been reported on by several authors. Loubele et al. (2008) compared liner measurements taken on small-field CBCT and multi-slice CT images, finding a 0.06 mm (± 1.23) width and a -0.09 mm (± 1.64) height variation from manual alveolar bone measurements. Micro millimetre accuracy was found when comparing CBCT and physical measurements taken on dried skulls (Kobayashi et al., 2004, Timock et al., 2011), with a low level of width (0.8–1 %) and height (2.2 %) variation (Marmulla et al., 2005) and measurement deviations (0.13 mm ±0.09) (Mozzo et al., 1998) when a pre-calibrated model was scanned. Although it can be concluded that CBCT systems render anatomical measurements reliably and are an appropriate tool for linear measurements (Patcas et al., 2012), the level of accuracy and inter-operator error may be affected by visual limitations, or when measuring small cross-sectional bone dimensions (Patcas et al., 2012, Leung et al., 2010, Cao et al., 2017, Wood et al., 2013). This is particularly important when immature or newly forming bone tissue may have a reduced bone density, which increase the risk of observational errors (Marmulla et al., 2005, Januario et al., 2011). There is a specific risk of greater inaccuracies, when measuring small width or thin bone height dimensions (Hilgers et al., 2005) and alveolar bone wall thickness (Molen, 2010, Timock et al., 2011). To minimise this risk of CBCT interpretation errors, this study utilised a grey scale pixel density to delineate the bone margin. This was particularly useful when determining the position and thickness of the buccal wall, as this anatomical

surface was often visually indistinct. This methodology indicated that the study population had a post extraction buccal socket width of above 1mm at the crestal, 5mm and 10mm socket depth positions for enrolled patients. These measurements corresponded with the 0.83mm to 1.05 mm coronal (Nowzari et al., 2012, Vera et al., 2012), and 1.08mm mid root (5mm) alveolar width dimensions reported by (Morjaria et al., 2014, Morad et al., 2014). Whilst Braut et al. (2011) and El Nahass and Naiem (2015) observed that the facial alveolar bone was absent in 25.7% - 75% of maxillary central incisor teeth, with Januario et al. (2011) and Ghassemian et al. (2012) reporting that less than 50% of teeth in the anterior maxillary had a buccal bone wall thickness greater that 0.5m, no evidence of bone dehiscence or fenestration was observed in this study. This variation may be due to the study inclusion criteria, which required patients to have an average to thick biotype, and an uncompromised socket contour.

6.7 Conclusion

GBR and SS ARP was found to be effective at limiting vertical alveolar bone loss, when compared with an unassisted healing Control Group. The buccal vertical dimensional change with GBR was limited. GBR was more efficient at preserving the mid-SA area. The null hypothesis (H_0) was therefore rejected for GBR ARP.

Chapter 7

Soft Tissue Contour Changes and Healing Characteristics Following ARP

Material And Methods

7.1 Introduction

The SS ARP technique was originally described using a Free Gingival Graft (FGG) to seal the extraction socket (Landsberg and Bichacho, 1994), as it was associated with reducing the adverse functional and volumetric gingival changes during healing (Jung et al., 2004). The presence of a FGG was recorded as positively influencing the anatomical and histological characteristics of the gingival tissue (Horváth et al., 2013, Vignoletti et al., 2014, Wang and Lang, 2012, De Risi et al., 2015, Morjaria et al., 2014), as it helped to establish an idealised functional, biologic and aesthetic foundation (Jung et al., 2004, Seibert and Salama, 1996). Resorbable allograft materials have now been advocated as an alternative seal, promoting a comparable stabilisation of the blood clot and protection of the underlying graft material (Bartee, 2001, Jung et al., 2004, Araujo et al., 2015), without the limitations of increased healing time, patient morbidity, or issues associated with the quality and texture of the graft matrix (Thoma et al., 2009, Soileau and Brannon, 2006, McGuire et al., 2008). Mucograft® is a collagen-based matrix, which is derived from a xenogenic origin. The matrix is purported to have a haemostatic effect, early wound stabilisation, chemotactic properties to attract fibroblasts, and semi-permeability (Postlethwaite et al., 1978) to promote revascularisation. Based on these favourable biological outcomes, Hämmerle and Jung (2003) proposed that the matrix was a viable material to promote an increase in the width and volume of keratinized tissue around teeth. Although collagen SS grafts materials have been proposed as a solution to many of the reported limitations of tissue derivative alternatives, the evidence of their suitability remains in-substantive (Postlethwaite et al., 1978, Cardaropoli et al., 2014, Jung et al., 2013a).

7.2 Horizontal contour change

An upper alginate impression was taken to record the baseline morphology of the tooth and gingival contour, prior to tooth extraction. A further alginate impression was taken at 4 months healing, with the working casts fabricated using Type IV stone. After drying and trimming of both the pre-extraction and 4 months casts, both models were optically scanned using the Nobel Procera scanning unit (Optimet Nobel Procera 2G scanner). The scans were then imported into the DTX Design control software (GMT 50125 GB © Nobel Biocare Services AG, 2017). Any missing scan data was subsequently added in with secondary scans. The completed 3D optical image was then inspected and cropped to remove any accessory anatomy, outside of the area of investigation. The pre-extraction and 4 months optical scans were then digitally fused by the DTX programme, using 6 fixed reference points on each model. The reference points were identified on a rigid anatomical structure (cusp tips), that would not undergo distortion when captured by the alginate impression. The DTX software then merged the scanned images according to a “best fit” algorithm. If the fit of the dentition in the remaining dentition was seen to be outside of 0.1mm, then the merged image was rejected, and additional reference positions were

added to improve coherence. Manual manipulation of the images was also undertaken to ensure best fit, if required (*Fig. 24*).

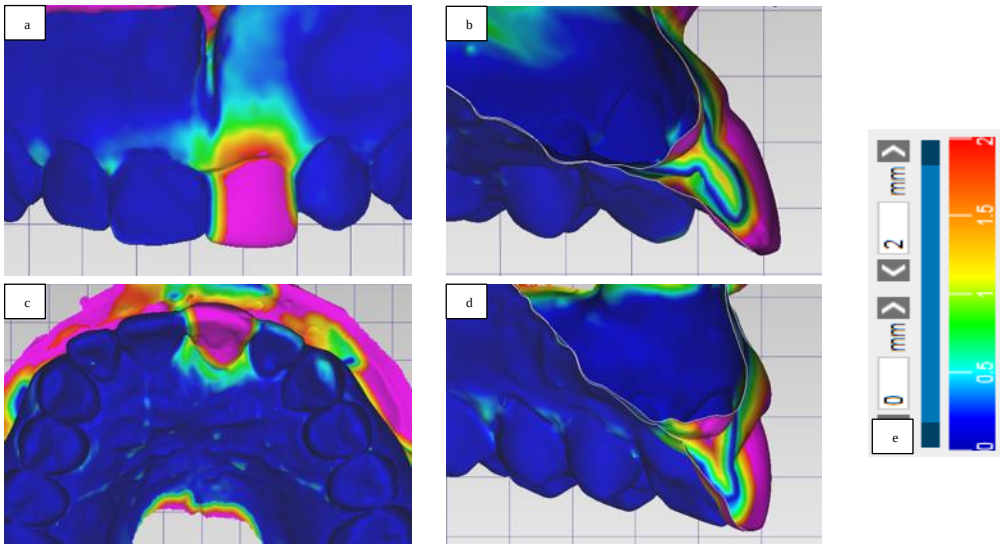


Figure 23 - *Pictures of superimposition of the optical scans taken prior to tooth extract and 4 months healing. (a) Buccal contour change in GBR group. (b) Cross-sectional midline view of contour change in GBR group. (c) Palatal contour change in the SS group. (d) Cross-sectional midline view of contour change in SS group. (e) Colour index demonstrating the amount of dimensional change (blue = 0.0 mm and red =2.0 mm).*

A cross sectional view of the overlapped images was then produced, with the image recorded at right angles to the long axis of the root and the buccal profile of the gingival margin. The difference in the horizontal contour change of each cast was recorded in the mesial papilla, mid root and distal papilla positions.

The alveolar ridge horizontal contour change was calculated at a coronal (gingival margin) and apical (5mm apical) reference position, using the long axis of the root for alignment (*Fig. 25*). The dimension contour change was calculated by first determining a tangential plane on the healed alveolar ridge, where a corresponding normal vector (right angles to the tangential plane) transected either the coronal or apical reference positions. The Coronal Horizontal (CHC) or Apical Horizontal Contour change (AHC) was determined by measuring the length of the magnitude from the healed alveolar ridge to the coronal and apical reference points, aligned along the direction of the corresponding normal vector (*Fig. 26*). Measurements were taken on both the buccal and palatal aspects of the extraction site (*Fig. 27*).

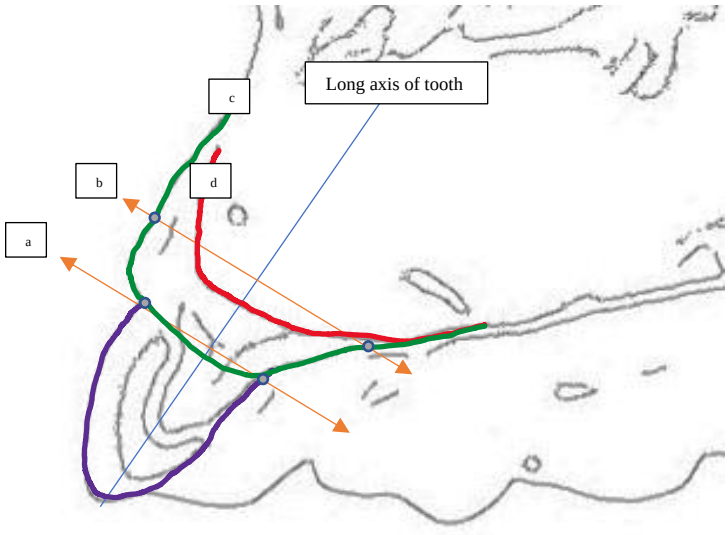


Figure 24. *Diagram showing coronal and apical reference position for horizontal contour change measurement. (a) coronal measurement position (CHC). (b) Apical 5mm position (AHC). (c) Original external contour (Green line). (d) Ridge contour at 4 months (Red line).*

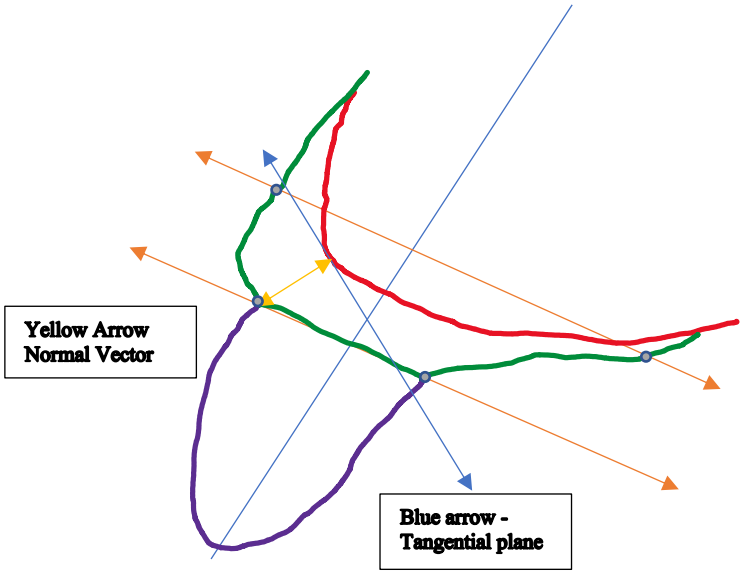


Figure 25. *Diagram demonstrating the normal vector and tangential plane used to measure the CHC change.*

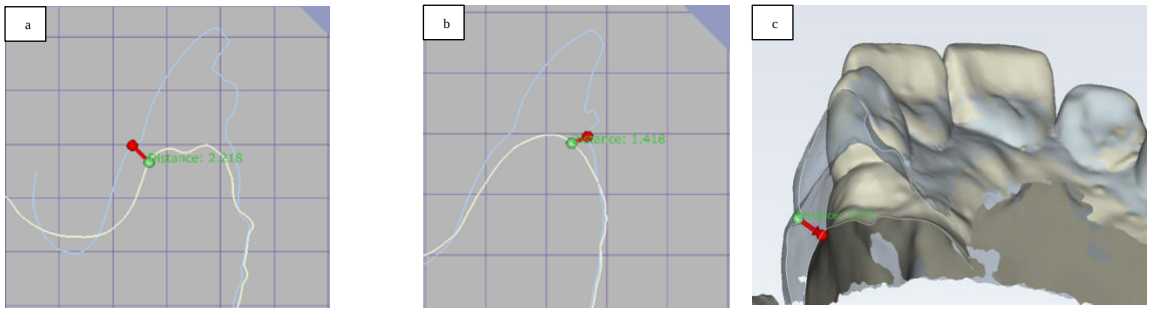


***Figure 26**. Cross-sectional mid-socket superimposed optical scans, measuring the buccal and palatal CHC tangential plane measurements. (a) Mid-buccal CHC on GBR case. (b) Mid-palatal AHC on SS case. (c) Image of two fused optical scans, with CHC measurement of SS case.*

7.3 Accuracy of the optical scan

The accuracy and reproducibility of the optical measurements was tested in a calibration exercise. The examiner produced ten alginate impressions of a reference dental model, with each impression cast in stone. The dried models were then optically scanned on five separate occasions and the 3D image files uploaded into the DTX software. The accuracy of the new stone replica model and the reproducibility of the optical scans was examined at 8 sites, by fusion of the optical scans from the reference and replicated stone casts. A colour mask was then applied, which acted to identify any dimensional change in the range of 0 to 2mm on the 8 marked test sites. Comparison of the casts indicated a ≤98% agreement at 0.1mm, between the original and duplicate casts and a ≤99% agreement with repeated optical scans of the stone casts. The alginate impression produced a replication error of less than of ≤ 0.1mm, when the reference and duplication model were compared (Fig. 28).

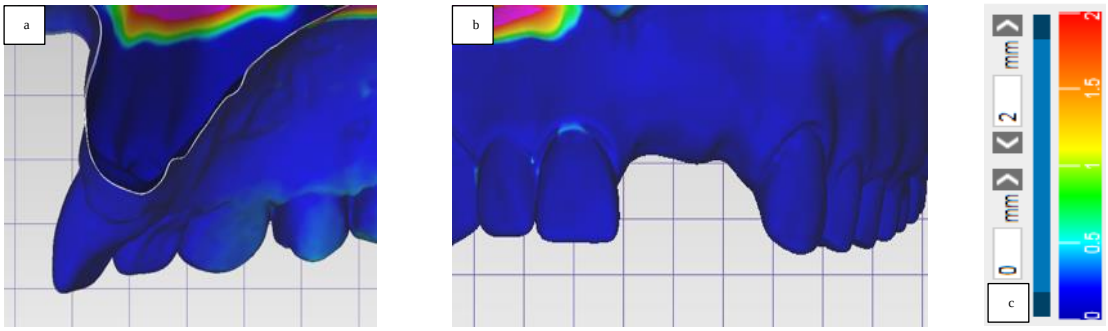


***Figure 27**. Images of superimposed optical scans during accuracy testing. (a) Cross-sectional mid-socket view. (b) Buccal view. (c) Colour index demonstrating the amount of dimensional change (blue = 0.0 mm and red =2.0 mm).*

7.4 Vertical dimensional change

An intra-oral stent was manufactured as described in paragraph 13.2.2. The tooth planned for extraction was sectioned from the cast and the model trimmed to the buccal and palatal gingival contour. If the original crown mas missing or damaged, a diagnostic wax-up of the crown was created as an alternative. A thermoplastic suck-down stent was adjusted to the outlined of the original gingival contour and filled with an acrylic material. The stent was designed to be used as a stable intraoral reference, to enable the measurement and comparison of vertical alveolar dimensional changes, recorded immediately after tooth extraction and following 4 months of healing. Mesial, Mid and Distal reference points were marked on the buccal and palatal aspects of the stent, with a depressed groove cut in the thermoplastic matrix along the vertical axis of the crown. These grooves acted to ensure consistency in the measurement of the buccal alveolar ridge height (BARH) and the palatal alveolar ridge height (PARH) dimensional change (*Fig. 29 and 30*).

The BARH and PARH measurements were initiated from the base edge of the buccal and palatal surfaces of the stent, extending to the first contact point on the gingival tissue margin, using a 0.5mm scale. The change in the Mesial (M) and Distal (D) papilla height was also calculated, recording the vertical distance between the base of the surgical stent, which had been shaped to follow the contour of the original gingival papilla and the tip of the residual papilla present at 4 months healing.

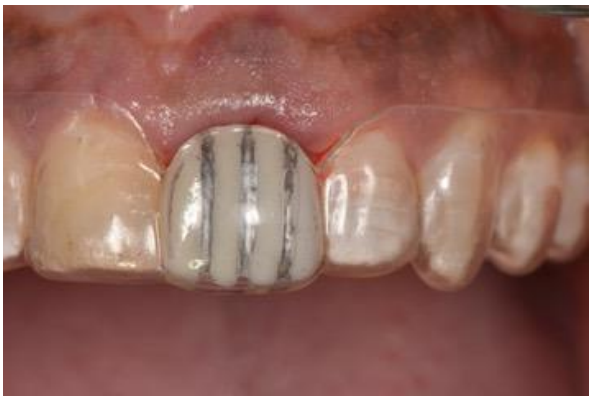


***Figure 28**. Picture of measurement stent in place immediately following tooth extraction. The picture demonstrates the three buccal measurement positions and minimal gingival contour change following tooth extraction.*

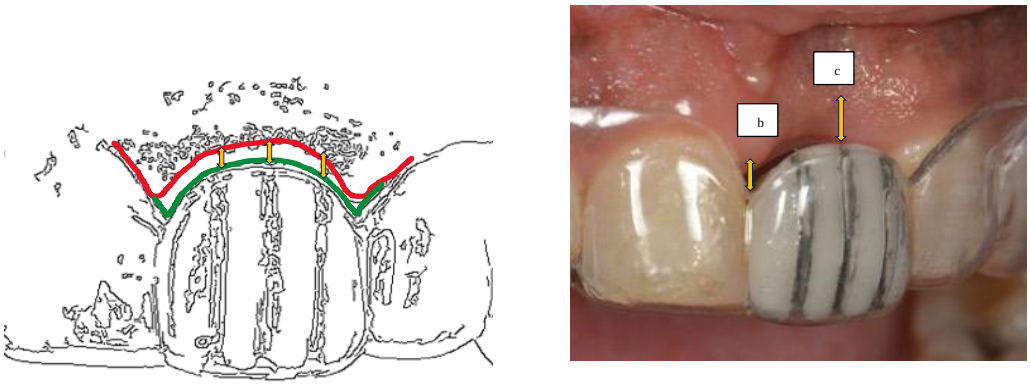


Figure 29. *Image and picture demonstrating BARH and mesial papilla recession following 4 months of healing. (a) Mesial, Mid and Distal vertical dimensional change. (b) Mesial papilla recession. (c) BARH measurement.*

7.5 Horizontal and vertical extent of the gingival tissue contour change

Following digital fusion of the post extraction and 4 months optical scans, a colour mask was applied to outline the extent of the dimensional change (vertical and horizontal) on the buccal and palatal/lingual aspect of the extraction site (*Fig. 31*). A measurement tool was used in the DTX programme, to calculate the extent of the vertical and horizontal tissue remodelling, observed from the colour mask. If the tissue changes extended into the unattached mucosa, the lowest contour change at the base of the sulcus was used as the measurement position.

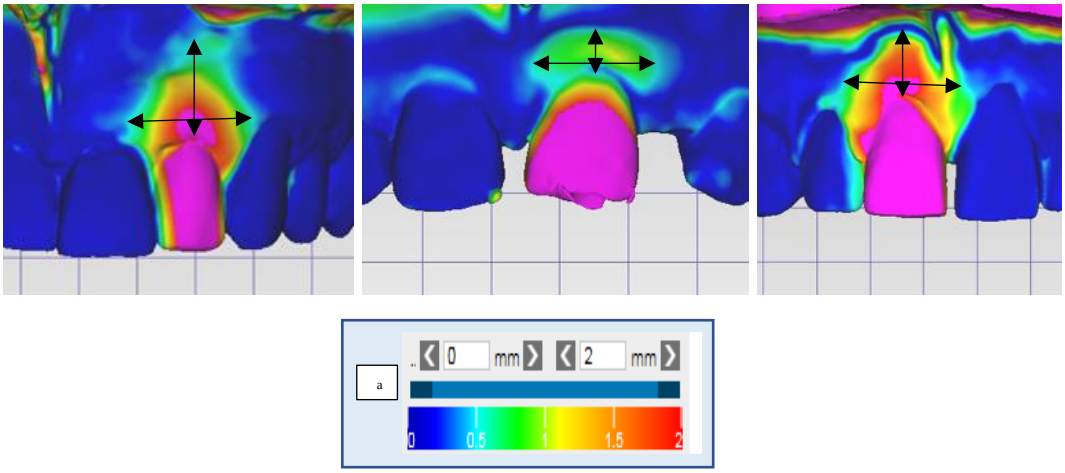


Figure 30*. Three optical scans demonstrating the extent of the buccal and palatal tissue remodelling following 4 months of healing. (a) Colour index demonstrating the amount of dimensional change (blue = 0.0 mm and red =2.0 mm).*

7.6 Gingival tissue thickness

The optical scans produced at the pre-extraction appointment and 4 months healing, were independently fused with their corresponding CBCT radiograph, using the DTX Design smart fusion algorithm. The combined image was then scrutinised, with the gingival margin thickness (GT) measured at the Mesial, Mid and Distal reference on the radiographic stent, at a point 5mm below the stent margin (*Fig. 32*). A comparison of the initial and 4 months healing dimensions was undertaken for the SS, GBR and Control groups, to determine if the thickness of the gingival tissue changed following ARP or unassisted healing.

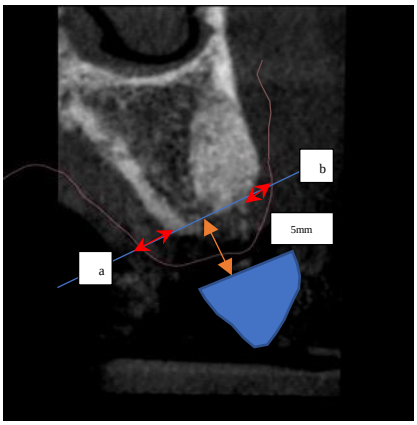


Figure 31. *Image indicating the superimposed optical and CBCT scans and the gingival margin thickness measurement calculated at 5mm from the radiopaque reference stent. (a) Palatal gingival thickness. (b) Buccal palatal thickness.*

7.7 Keratinised tissue width

The keratinised tissue width was calculated as a linear measured using a UNC 15 periodontal probe (0.5mm scale), with the linear dimension recorded between the crest of the buccal gingival margin and the muco-gingival junction. The most coronal aspect of the buccal healed ridge was used as the reference position at 8 weeks and 4 months of healing. The measurement stent was used to identify the Mesial, Mid and Distal reference positions, also directing the vertical long axis for the measurement (*Fig. 33*). The change in the width of the gingival keratinised tissue (KT), was calculated by extracting the initial KT width measurement, from the dimension recorded at 8 weeks and 4 months of healing.

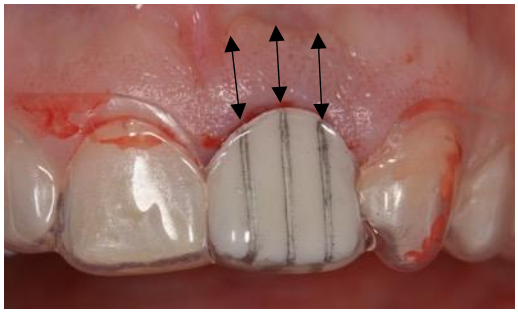


Figure 32. *Reference positions for the measurement of the keratinised tissue width, with an arrow indicating the MID-B keratinised width.*

7.8 Power calculation

The power calculation for this RCT was based on the primary outcome measure of vertical radiographic dimensional change described in Chapter 5, section 9. Despite this, statistical analysis based on the number of patients included from the primary outcome, would be sufficient to identify statistical significance of this secondary outcome. This is because assuming a clinically relevant difference in bucco-palatal width of 1.5 mm, between the Control and augmented group and a control effect size of -3.7mm, with a standardised mean difference of 1.2mm (Festa, 2013), a test group size of 8, will have 90% power to detect a difference in means (using an independent samples t-test) at an alpha level of 5%. A sample size of approximately 14 per group will be utilised to allow for dropouts.

The standardised mean difference of 1.2mm in horizontal alveolar dimensions, between ARP and a non-treated site was chosen as it matches the effect size of 1.198mm (95% CI: -0.037 to 2.433) recorded in the systematic review undertaken in this thesis and the ARP horizontal changes reported on by the studies undertaken by Vance 2004 and Barone 2013.

7.9 Statistical analysis

All data was entered in a computer database, proofed for entry errors and loaded in the SPSS statistical software package (v.22). Tissue dimensions at tooth extraction and at 4 months healing, were recorded as a mean ± standard deviation for the three test groups.

Data normality was assessed by the Shapiro Wilk test (Shapiro and Wilk, 1965) and Levene's test of Variance (Levene, 1960). If the data was normally distributed the differences between the groups was assessed using parametric methods. If the assumptions were not fulfilled, non-parametric tests were used instead. Significance was set at $p < 0.05$.

Parametric Tests:

i) Independent samples t-tests for differences in means between groups.

ii) One-way fixed effect ANOVA. If a significant difference was observed between the groups from the one-way ANOVA, a Tukey's honestly significant difference post hoc analysis was performed to check which specific groups differed.

Non-Parametric tests:

i) Independent Wilcoxon rank sum test between groups.

ii) Kruskal–Wallis non-parametric one-way analysis of variance. If a significant difference was observed between the groups a post hoc analysis was performed using Dunn's procedure. A Bonferroni correction for multiple comparisons was used and adjusted *p*-values were presented.

The reproducibility of the clinical and optical measurements was tested in an intra-rater reliability calibration exercise. The examiner performed duplicated measurements in 10 randomly selected patients, with a minimum of a 15 min interval between measurements. The percentage agreement of measurements was then calculated, with the goal to obtain a $< 90\%$ reproducibility ≤ 0.5mm.

Chapter 8

Soft Tissue Contour Changes and Healing Characteristics Following ARP
Results and Discussion

8.1 CHC and AHC contour changes

The SS, GBR and Control groups all suffered horizontal tissue loss, following tooth extraction. The GBR recorded the lowest level of mid-buccal CHC change (-1.65mm SD 0.69), with the SS and Control groups reporting a higher mid-buccal CHC change of -2.48mm (SD 0.68) and -2.31mm (SD 0.76). A statistic difference in the Mid-buccal CHC tissue loss was recorded when comparing the GBR and SS (p=0.02) and the GBR and Control groups (p=0.048). No statistical difference was found when horizontal contour changes were measured in the mesial or distal buccal positions. The mid-buccal AHC reduction was -1.55mm (SD 0.6) for SS, -1.45mm (SD 0.62) for GBR and -1.64mm (SD 0.62) for the Control. No statistic differences were recorded between the GBR, SS and control groups at the mid-buccal AHC position,

Palatally, a lower levels of horizontal tissue loss were recorded at both the CHC and AHC positions when compared to the buccal measurements. The Mid-palatal CHC position demonstrated -1.5mm (SD 0.83) of tissue loss when using a SS technique, -1.2mm (0.76) for GBR and -1.31mm (SD 0.5) for the Control group. No statistic difference was found when comparing the SS, GBR or Control Mid-palatal contour reduction at both the CHC and AHC positions.

The mean buccal and palatal horizontal contour changes at the CHC and AHC positions, are summarized in Table 29. The intra-rater reliability for the measurement was assessed as 0.92 (0.5mm accuracy).

Table 29. *Buccal and Palatal mean cervical horizontal contour (CHC) and apical horizontal contour AHC change (mm)*

ARP Technique	Mesio-buccal CHC	Mesio-buccal AHC	Mid-buccal CHC	Mid-buccal AHC	Disto-buccal CHC	Disto-buccal AHC	Mesio-palatal CHC	Mesio-palatal AHC	Mid-palatal CHC	Mid-palatal AHC	Disto-palatal CHC	Disto-palatal AHC
SS	-1.63	-1.24	-2.48	-1.55	-1.76	-1.19	-1.12	-0.34	-1.50	-0.32	-1.55	-0.36
SD	0.50	0.62	0.68	0.77	0.60	0.67	0.49	0.31	0.83	0.39	0.50	0.39
GBR	-1.23	-0.82	-1.65	-1.11	-1.45	-0.85	-0.87	-0.36	-1.2	-0.39	-1.24	-0.26
SD	0.69	0.69	0.69	0.83	0.63	0.48	0.74	0.38	0.74	0.49	0.44	0.43
Control	-1.54	-1.08	-2.31	-1.56	-1.64	-1.12	-1.12	-0.62	-1.31	-0.59	-1.33	-0.56
SD	0.54	0.43	0.76	0.56	0.62	0.44	0.53	0.39	0.5	0.75	0.65	0.38
One-way ANOVA	0.16	0.23	0.02	0.19	0.3	0.16	0.29	0.03	0.35	0.35	0.02	0.11
F test	1.91	1.5	0.44	1.73	1.23	1.89	1.24	3.2	1.06	1.06	3.98	2.25
Tukey's HSD (P) 0.05			P=0.02 SS vs. Control P=0.048 GBR vs. Control					P=0.04 SS vs. Control			P=0.02 SS vs. GBR	

Index: Mesio, mesial; Mid, Middle; Disto, Distal, CHC, cervical horizontal contour; AHC and apical horizontal contour (mean and SD in mm).

8.2 BARH and PARH tissue remodelling

All three test groups demonstrate a measure of vertical tissue loss, immediately following tooth extraction. The SS technique demonstrate the least mid BARH (-0.32mm SD 0.61) or mid PARH (-0.71mm SD 0.6) vertical change, with GBR recording the most mid BARH (-0.82mm SD 0.6) and mid PARH (-0.64mm SD 0.6) transformation. ANOVA analysis did not reveal a statistic difference between the SS, GBR or Control groups, immediately following extraction of the tooth. The level of vertical tissue loss then increased in both the SS and Control groups at 8 weeks, with a subsequent regain, but overall loss of tissue height for both the SS and Control groups at 4 months of healing. The GBR group recorded a small gained in mid BARH at 8 weeks, but a reduction of -0.68mm (SD0.7) at 8 weeks, with this vertical dimension remaining stable at 4 months.

Palatally, GBR demonstrated a small loss in PARH, which remained relatively stable over the subsequent 8 weeks (-0.64mm SD 0.6) and 4 months (-0.61mm SD 0.66) healing period. The SS group recorded a mid BARH and mid PARH reduction of -1.21mm (SD0.93) and -1.14mm (SD 0.71) at 8 weeks, and -1.07mm (SD 0.76) and -1.07mm (SD 0.53) at 4-months. The Control group demonstrated -1.54mm (SD 0.69) and -1.5mm (SD 0.44) of mid BARH and mid PARH tissue loss at 8 weeks and -1.32mm (SD 0.82) and -1.46mm (SD 0.46) at 4 months.

A statistical difference was found when comparing the GBR mesial, mid-buccal and distal BARH and PARH dimensional changes, against both the SS and Control group changes (ANOVA $p < 00.5$), at 8 weeks and 4 months healing.

The mean buccal and palatal vertical reduction measurements are summarized in Table 30. The intra-operator reliability was assessed as 0.91 at $\leq$ 0.5mm accuracy.

Table 30 *– Buccal and palatal mean alveolar ridge height (ARH) Clinical Tissue Changes (mm)*

ARP Procedure		Vertical Measurements Following Tooth Extraction						Vertical Tissue Change At 8 Weeks						Vertical Tissue Change At 4 Months					
		Mesial BARH	**Mid BARH**	**Distal BARH**	**Mesial PARH**	**Mid PARH**	**Distal PARH**	**BARH Mesial**	**Mid BARH**	**Distal BARH**	**Mesial PARH**	**Mid PARH**	**Distal PARH**	**Mesial BARH**	**Mid BARH**	**Distal BARH**	**Mesial PARH**	**Mid PARH**	**Distal PARH**
SS	XlA	-0.14 (0.36)	-0.32 (0.61)	-0.18 (0.37)	-0.43 (0.51)	-0.71 (0.61)	-0.75 (0.94)	-0.86 (0.72)	-0.89 (0.92)	-1.07 (0.83)	-0.54 (0.77)	-0.43 (0.58)	-0.68 (0.93)	-0.75 (0.75)	-0.75 (0.96)	-1.14 (0.77)	-0.46 (0.77)	0.36 (0.63)	-0.64 (1.09)
	8 Weeks	-1.00 (0.73)	-1.21 (0.93)	-1.25 (0.82)	-0.96 (0.54)	-1.14 (0.71)	-1.43 (0.61)												
	4 Months	-0.89 (0.68)	-1.07 (0.76)	-1.32 (0.75)	-0.96 (0.63)	-1.07 (0.53)	-1.39 (0.74)												
GBR	XlA	-0.54 (0.5)	-0.82 (0.6)	-0.71 (0.64)	-0.71 (0.42)	-0.64 (0.6)	-0.57 (0.62)	-0.14 (0.57)	0.14 (0.63)	0.07 (0.73)	0.32 (0.46)	-0.04 (0.69)	-0.25 (0.75)	0 (0.75)	0.14 (0.74)	0.11 (0.79)	0.21 (0.61)	0 (0.55)	-0.32 (0.75)
	8 Weeks	-0.68 (0.67)	-0.68 (0.7)	-0.64 (0.6)	-0.39 (0.49)	-0.68 (0.6)	-0.82 (0.42)												
	4 Months	-0.54 (0.75)	-0.68 (0.87)	-0.61 (0.66)	-0.50 (0.68)	-0.64 (0.69)	-0.89 (0.49)												
Control	XlA	-0.32 (0.46)	-0.64 (0.71)	-0.39 (0.63)	-0.29 (0.47)	-0.93 (0.55)	-0.57 (0.55)	-0.89 (0.65)	-0.89 (0.56)	-0.89 (0.86)	-0.82 (0.69)	-0.57 (0.78)	-0.64 (0.57)	-1.04 (0.79)	-0.68 (0.66)	-0.79 (0.67)	-0.86 (0.53)	-0.54 (0.82)	-0.75 (0.5)
	8 Weeks	-1.21 (0.7)	-1.54 (0.69)	-1.29 (0.8)	-1.11 (0.44)	-1.50 (0.44)	-1.21 (0.47)												
	4 Months	-1.36 (0.81)	-1.32 (0.82)	-1.18 (0.67)	-1.14 (0.32)	-1.46 (0.46)	-1.32 (0.42)												
One-way ANOVA (p) 0.05		0.077	0.13	0.06	0.06	0.42	0.75	0.004	0.001	0.001	0.001	0.12	0.27	0.001	0.009	0.03	0.003	0.117	0.366
F Test								5.92	9.53	8.11	11.47	2.26	1.35	6.76	5.4	10.45	9.84	2.26	1.03
Post Hoc Tukey's HSD (P)0.05								0.016 SS Vs. GBR 0.01 GBR Vs. Cont	0.001 SS Vs. GBR 0.001 GBR Vs. Cont	0.001 SS Vs. GBR 0.008 GBR Vs. Cont	0.003 SS Vs. GBR 0.001 GBR Vs. Cont			0.036 SS Vs. GBR 0.033 GBR Vs. Cont	0.014 GBR Vs. SS 0.026 GBR Vs. Cont	0.001 GBR Vs. SS 0.008 GBR Vs. Cont	0.022 SS Vs.GBR 0.001 GBR Vs. Cont		

Index: Mid, Middle; BARH, buccal alveolar ridge height and PARH, palatal alveolar ridge height (mean and SD measurements in mm)

8.3 Optical vertical and horizontal extent of tissue remodelling

The vertical extension of the buccal and palatal tissue remodelling was similar for all three test groups. A mean value of 9.52mm (SD 3.84) of vertical change was recorded in the SS group, 8.18mm (SD 3.03) in the GBR group, with 8.7mm (2.95) found in the Control. Slightly greater palatal vertical tissue remodelling was recorded in the Control group (6.49 mm SD 2.92) when compared to the 5.13mm (SD 4.25) for SS and 4mm (SD 4.43) for GBR. The extent of the buccal horizontal tissue loss was similar for the SS, GBR and control groups (11.98mm SD 3.56, 11.78mm SD 3.99 and 12.41mm SD 3.07) but palatally, the Control group recorded a slightly greater change of 8.27mm (SD 2.98) when compared to the 6.49 mm (SD 2.92) for SS and 5.29 (SD 5.01) mm for GBR. ANOVA analysis did not reveal a statistical difference in the vertical and buccal extent of the tissue loss for the three test groups (Table 31).

Table 31 *– The Extent of the Vertical and Horizontal Buccal and Palatal Tissue Mean Changes (mm)*

ARP Procedure	Vertical height of buccal tissue remodelling	Width of buccal tissue remodelling	Vertical height of palatal tissue remodelling	Width of palatal tissue remodelling
SS	9.52 (SD 3.83)	11.98 (SD 3.56)	5.13 (SD 4.25)	6.49 (SD 2.96)
GBR	8.18 (SD 3.03)	11.78 (SD 3.99)	4.00 (SD 4.43)	5.29 (SD 5.01)
Control	8.77 (SD 2.95)	12.41 (SD 3.07)	6.54 (SD 4.14)	8.27 (SD 2.98)
One-way ANOVA	0.349	0.84	0.29	0.12
F Test	1.07	0.17	1.4	0.89
Tukey's HSD (P)0.05				
Index: Mean and SD measurements in mm				

8.4 Gingival tissue thickness (GT)

Localised variations in the dimension of the GT were found in the SS, GBR and Control groups. The buccal Mid-socket region recorded a small reduction in GT of-0.42mm (SD 1.59) with SS, -0.03mm (SD0.65) with GBR and -0.13mm (SD 0.82) in the Control. The Mid-socket palatal thickness recorded an increase in GT of 0.18 (SD 1.27) with GBR and 0.4mm (SD 0.45) in the Control. SS recorded a reduction of GT of -0.59mm (SD 1.14) (Table 32). A Kruskal-Wallis one way ANOVA analysis recorded a statistical difference in the GT when comparing the SS and Control groups in the Mid-P aspect (p 0.01).

Table 32 *– Mean Gingival Tissue Thickness Changes after 4 Months Healing (mm)*

ARP Procedure	Mesial Buccal 5mm	Midline Buccal 5mm	Distal Buccal 5mm	Mesial Palatal 5mm	Midline Palatal 5mm	Distal Palatal 5mm
SS	0.06 (SD 0.72)	-0.42 (SD 1.59)	0.06 (SD 0.5)	-0.14 (SD 0.87)	-0.59 (SD 1.14)	-0.36 (SD 0.75)
GBR	0.42 (SD 0.69)	-0.03 (SD 0.65)	-0.02 (SD 0.84)	0.16 (SD 1.11)	0.18 (SD 1.27)	0.29 (SD 1.79)
Control	0.11 (SD 0.68)	-0.13 (SD 0.82)	0.23 (SD. 0.5)	0.63 (SD 1.48)	0.40 (SD 0.45)	-0.14 (SD 0.68)
One-way ANOVA	0.389	0.65	0.61	0.255	0.04	0.37
F Test	0.967	0.435	0.5	1.417	3.4	1.01
Tukey's HSD (p) 0.05					SS Vs. GBR p=0.04	
Index: Mean and SD measurements in mm						

8.5 Keratinised Tissue Width

The mean width of the keratinised tissue margin in the mid-buccal position was similar in the GBR (4.54 mm SD 0.77), SS (4.86 mm SD 1.3) and Control (4.71mm SD 1.17) groups at enrolment. All three test groups demonstrated a small reduction in the KT dimensions at 8 weeks of healing, with the SS technique recording the biggest change (-0.29mm SD 1.09). At 4 months healing, the GBR group recorded a slight increase in KT width (0.14mm SD 0.77), with the SS and Control groups demonstrating a small loss (-0.29 SD 1.09 and -0.25mm SD 0.73). The mean and standard deviation values for the changes in keratinised tissue dimensions for the SS, GBR and Control groups are detailed in Table 33.

ANOVA analysis revealed no statistical difference between the SS, GBR and Control KT measurements at 8 weeks and 4 months of healing.

Table 33 *– Mean Keratinised Tissue Dimensional Change During Socket Healing (mm)*

ARP Procedure	At Tooth Extraction			Change in Keratinised Tissue Dimension At 8 Weeks			Change in Keratinised Tissue Dimension at 4 Months		
	Mesial	Mid	Distal	Mesial	Mid	Distal	Mesial	Mid	Distal
Socket Seal	5.00 SD (1.03)	4.86 SD (1.3)	5.32 SD (1.23)	-0.25 SD (1.09)	-0.29 SD (1.09)	-0.18 SD (0.92)	-0.29 SD (1.16)	-0.29 SD (1.09)	-0.43 SD (0.94)
GBR	4.75 SD (0.94)	4.54 SD (0.77)	5.04 SD (0.84)	-0.04 SD (0.81)	-0.18 SD (0.91)	-0.07 SD (0.99)	0.07 SD (0.73)	0.14 SD (0.77)	0.11 SD (1.15)
Control	5.00 SD (1.09)	4.71 SD (1.17)	5.07 SD (1)	0.10 SD (1.06)	-0.21 SD (1.35)	0.04 SD (1.1)	0.07 SD (0.77)	-0.25 SD (0.73)	-0.21 SD (1.15)
One-way ANOVA (p) 0.05				0.62	0.83	0.86	0.46	0.63	0.24
F				0.478	0.188	0.153	0.788	0.473	1.49
Tukey's HSD (p)0.05									
Index: Mean and SD measurements in mm									

8.6 Periodontal parameters

FMPS and FMBS scores were recorded and maintained at less than 10%, for all patients during treatment (Donos, 2018, Monje et al., 2019). The SS group demonstrated buccal mesial and distal papilla REC of 0.5mm (SD 0.48) and 0.54 mm (SD 0.5) at 8 weeks of healing. Palatally a lower level of REC was recorded 0.29mm (SD 0.61) and 0.36mm (SD 0.63). The GBR and Control groups demonstrated negligible proximal REC at 8 weeks.

At 4 months healing, the SS group recorded a higher level of buccal mesial and distal REC at 0.68mm (SD 0.54) and 0.54mm (SD 0.5) and palatal REC of 0.54mm (SD 0.69) and 0.5mm (SD 0.52). GBR now recorded evidence of buccal REC of 0.46mm (SD 0.5) and 0.43mm (SD 0.47) and palatal REC of 0.46mm (SD 0.5) and 0.54mm (SD 0.5). The Control recorded buccal REC of 0.57mm (SD 0.51) and 0.43mm (SD 0.68) and palatally REC of 0.25mm (SD 0.55) and 0.43mm (SD 0.55). Proximal REC at the mesial and distal papilla sites was not statistically different (Kruskal-Wallis Test) at either 8 weeks or 4 months healing, when comparing the GBR, SS and Control groups.

8.7 Discussion

A diversity in outcomes following ARP procedures has been reported in several Cochran reviews (Atieh et al., 2012, Burch, 2021, Atieh et al., 2021) and again found in the systematic review published by Horváth et al. (2013). These reports indicated that there is a lack of evidence demonstrating the superiority of a particular ARP technique. They questioned whether different ARP surgical techniques, independently affect the intra-oral dimension and the keratinised tissue characteristics at the healed extraction site (Moghaddas et al., 2012, Tan et al., 2012, Thoma et al., 2020b). This RCT established that both GBR and SS ARP techniques were effective at reducing the level of vertical contour change, with reduced horizontal remodelling only found with GBR. Both GBR and SS ARP techniques, were noted to affect the gingival tissue healing characteristics at 8 weeks and 4 months. The recorded reduction in the vertical and horizontal contour changes, could potentially influence the ability to place an implant fixture and the characteristics of the gingival tissue surgical flap at Type-3 implant placement.

8.7.1 Optical horizontal contour changes

Optical comparison of dental casts undertaken after 4 months healing, indicate that whilst ARP modifies the healing characteristics of the extraction socket, remodelling could not be prevented (Thalmair et al., 2013). At 4 months healing, the extent of the mid-buccal CHC and AHC remodelling in the SS and Control test groups was similar, with additional tissue loss recorded in the SS mid-palatal CHC area. Whilst the comparison of optical scans does not identify if the contour change is attributed to either the bone or soft tissue healing pattern, the examination of the SS gingival thickness measurements, indicate

that SS was associated with more thinning of both the buccal and palatal gingival tissues, when compared to negligible or positive changes observed with GBR and the Control. This observation indicates that soft tissue thickness compounds the horizontal dimensional changes observed in the SS group.

GBR appeared to offer some clinical advantage over the SS and Control techniques, being effective at reducing the mid-buccal and mid-palatal CHC (p=0.2) and AHC (p=0.48) contour changes. This reduction may potentially be attributed to the GBR membrane being more effective at stabilisation of the nascent clot, promoting the migration of adjacent cells (Liu and Kerns, 2014), revascularisation and epithelialisation of the extraction site tissue and osteogenesis in the socket (Omar et al., 2019, Hämmerle et al., 2014, Retzepi and Donos, 2010, Donos et al., 2004). The GBR membrane may also be more substantive as a tissue barrier, promoting GBR (Retzepi and Donos, 2010, Donos et al., 2004), or may play a part in improved healing, through the bioactive membrane concept (Omar et al., 2019, Retzepi and Donos, 2010, Cardaropoli et al., 2005, Calciolari et al., 2018b). This theory supports that the presence of a barrier membranes may improve the haemostatic effect, early wound stabilisation, chemotactic ability to attract fibroblasts, and revascularisation of the augmented socket site.

The dimensional contour changes obtained by Schneider et al. (2014) and Fischer et al. (2018) indicate a lower mid-buccal contour reduction to the results observed in this study. Schneider et al. (2014) found a buccal horizontal contour change of -1.8mm ±0.8 with SS and a reduction of -1.2mm ± 0.5 for GBR. Fischer et al. (2018) observed a lower buccal change for both of SS (-0.87mm ±0.71) and GBR (-1.26mm ±0.94). The contour reduction for unassisted healing in both of these studies was -1.8mm ±0.8 and -2.15mm ±1.34, which was lower than the measurement recorded in this RCT.

Caution must be used when attempting to compare the horizontal contour measurements obtained from different studies, as variation in the dimensional change may result from differences in the measuring positions (Schneider et al., 2014, Thalmair et al., 2013) and the methodology adopted (Jonker et al., 2021). The degree of profilometric contour change was found to be lower when the horizontal measurement was taken several milometers below the socket margin (Jung et al., 2013b), emulating the reduction observed when comparing the CHC and the AHC position. This variability and inconsistency in the horizontal measurement position was identified by Schneider et al. (2014), as he varied the horizontal measurement position due to vertical tissue loss. This inconsistency in measurement points may explain the difference observed when comparing the results from contour studies.

8.7.2 Comparison of radiographic and contour measurement studies

The comparison of contour and radiographic dimensional changes should also be undertaken with caution, as the external soft tissue contours do not always conform to the resorption patterns of the alveolar bone (Jung et al., 2013b). A radiographic width reduction of -1.2 mm (-17.4%) when using a

SS ARP technique with a collagen matrix (Jung et al., 2013b), or a -2.53mm reduction with a GBR ARP technique using a bovine xenograft and acellular dermal matrix graft (Fernandes et al., 2011), is not directly comparable to profilometric contour change. This is because tissue healing can result in tissue invaginations, soft tissue volume changes and variation in the thickness of the keratinised gingival tissue (Thoma et al., 2020b). An appreciation of the complexity of the post extraction healing process is required, as a 7.5-fold increase in facial soft tissue thickness has been reported in thin biotype patients, which did not match or reflect the underlying bone anatomy (Chappuis et al., 2015).

Whilst optical scanning techniques have now been recognised as an effective method to examine topographical changes, only recently published studies have adopted this methodology. Variations have also been noted in the methodology of the dimensional measurement (Thalmair et al., 2013, Ivanova et al., 2019). Differences have included the horizontal angulation of the measurement, whether the measurement is taken at right angles to the root axis or the alveolar ridge contour and whether consideration is given to the curved profile of the healed alveolar process. This study, by using a tangential plane and normal vector as the measurement axis, attempted to limit this error. Promoting a more accurate measurement of the horizontal contour change, based on a measurement taken at 90 degrees to the curvature of the residual alveolar ridge.

8.7.3 Vertical clinical tissue changes

The results of this chapter indicated that a SS ARP technique using a collagen matrix, did not decrease the amount of vertical tissue loss in the mid-buccal area, when compared to the Control group at 8 weeks (-0.89mm), but demonstrated a lower level of vertical reduction at 4 months (-0.75mm compared to -0. 68mm). This finding would appear to contradict the SS results from Jung et al., (2013b) and Meloni et al. (2015). Jung et al., (2013b) reported no vertical change when using a SS technique, with Meloni et al. (2015) finding a greater vertical change of -1.6mm.

GBR demonstrated a mid-buccal vertical tissue loss of -0.82mm at 8 weeks, with a slight recovery of vertical tissue height to -0.68mm over 8 week to 4 months healing period. Although some GBR studies have reported a gain in vertical bone height following ARP (Jung et al., 2013b, Vance et al., 2004), a small loss of vertical bone height was more regularly observed (Barone et al., 2008, Cardaropoli and Cardaropoli, 2008, Crespi et al., 2009a, Jung et al., 2013b), with a range of -0.4mm to -1.5mm vertical tissue loss reported by (Mardas et al., 2011, Jung et al., 2013b, Barone et al., 2013c, Gholami et al., 2012). The second systematic review in this thesis indicated a pooled effect size of -0.467 mm (95% CI: -0.866 to -0.069) in the mid-buccal alveolar ridge height, which corresponds to the vertical tissue decrease observed in this RCT. The degree of vertical bone resorption was found to be less in the proximal areas, with a small level of variation noted between measurements taken at the mesial or distal

proximal positions. This reduction in mesial and distal vertical bone loss was also observed by (Barone et al., 2013b, Mardas et al., 2011).

The vertical difference between the GBR and the SS and Control groups was statistically significant and suggests that GBR provides a more stable foundation for adjacent gingival tissue regeneration at 8 weeks, whilst the SS and the Control underwent additional resorption over the 8 week to 4 month healing period.

SS and GBR were both found to have a lower level of PARH, when compared to the Control group, with the PARH dimensional changes observed to be lower than the BARH. This reduced palatal height change has been observed by other research studies (Fernandes et al., 2011, Jung et al., 2013b), whilst a gain in palatal vertical height has been reported after ARP by some authors (Barone et al., 2008, Barone et al., 2013a, Jung et al., 2013b).

8.7.4 Gingival tissue thickness changes

Removal of a failing tooth results in the creation of an open wound in the alveolar ridge and a deficiency in the gingival layer covering the bone. Soft tissue healing at the extraction site, is an important component of the remodelling process. Changes to the character and dimension of the local tissue have been reported during this healing process (Tarnow et al., 1996, Jemt, 1997, Schrott et al., 2009, Darby et al., 2009). The application of the ARP procedures frequently involves complex surgical flap manipulation, that may result in undesirable consequences to the gingival tissue healing. These changes may include disruption of the blood supply to the very thin labial bone plate, which may cause additional bone loss in the extraction site (Jung et al., 2004). Side effects include gingival marginal recession, loss of keratinized tissue, reduced interdental papillary height, reduced tissue thickness, alteration to the muco-gingival line (Engler-Hamm et al., 2011) and scarring of the soft tissues. These cumulative changes may lead to an undesirable topography, influencing the future aesthetic outcome of implant treatment (Landsberg, 2008).

This study found that the mid-socket buccal region demonstrated a small reduction in tissue thickness with GBR (-0.03mm SD0.65) and Control (-0.13 SD 0.82) test groups, which mirrors the observed tissue changes found in the studies undertaken by Iasella et al. (2003), Thoma et al. (2020a) and (Vance et al., 2004). The SS technique recorded a higher buccal (-0.42mm SD 1.59) and palatal (-0.59mm SD 1.14) reduction in gingival thickness measurements, this finding was found to be statistically significant in the Mid-palatal aspect ($p = 0.4$). This reduction may have a clinical significance if additional bone augmentation is required at implant placement.

Various invasive and non-invasive methods have been proposed to measure the gingival tissue thickness in the oral environment. These include direct measurement (Greenberg et al., 1976) and probe transparency methods (De Rouck et al., 2009). Although these techniques are simple and reproducible,

they can be affected by the precision of the probe placement, the angulation of the probe and the distortion of the tissue during the measurement (Fu et al., 2010). CBCT overlay of optical scans (Barriviera et al., 2009) Spata et al., 2018; Araújo et al., 2015; Chappuis et al., 2013; Jung et al., 2013b; Llanos et al., 2019) appear to be the least invasive method to measure gingival tissue thickness and offers a reliability and reproducible measurement (Eger et al., 1996). Whilst gingival tissue measurements based on CBCT and Optical superimposition have been found to be effective and reliable, they have not been validated against transmucosal probing or ultrasound measurements. Heterogeneity may also be associated with the impression technique, data acquisition and software superimposition method (Tavelli et al., 2021). This lack of consistency may introduce a risk of bias, when comparing the results of studies with different methodologies.

8.7.5 Extent of the buccal and palatal profile contour change

The extent of the buccal and palatal vertical and horizontal remodelling was generally similar in the GBR, SS and Control groups, indicative of a similar bone and soft tissue healing outline and profilometric contour change, following tooth extraction (Chappuis et al., 2017, Cosyn et al., 2021).

Whilst no statistical difference was detected in the vertical and horizontal profilometric measurements, a small clinical advantage was recorded when using GBR, which underwent the least horizontal 12.28mm (SD 4.21) and vertical 8.04 (SD 3.18) contour change. Whilst placement of the GBR membrane was associated with the requirement to raise a small flap at the extraction site, this local trauma and surgical intervention was not associated with additional tissue damage and horizontal contour change. The reduce mucosal change may have advantages in the final aesthetics of the implant crown (Noelken et al., 2018, Avila-Ortiz et al., 2014a, Araujo et al., 2015, Thoma et al., 2009) influencing the pink aesthetic score for the restoration.

8.7.6 Changes in keratinised tissue width

The application of GBR in ARP procedures has frequently been associated with flap manipulation that may result in additional undesirable side effects to the gingival tissue and an incision being made close to the flap. This surgical incision may deplete the blood supply to the very thin labial bone plate and potentially cause additional bone loss in the extraction site (Jung et al., 2004). The side effects described have included gingival marginal recession, loss of keratinized tissue, reduced interdental papillary height, reduced tissue thickness, alteration to the muco-gingival line (Engler-Hamm et al., 2011) and scarring of the soft tissues. These cumulative changes may lead to an undesirable topography and aesthetic contours of the healed socket, influencing the aesthetic outcome of implant treatment (Landsberg, 2008) (Chappuis et al., 2017),leading to the promotion of a SS technique

In this study, the dimensions of the keratinised tissue margin were similar in the SS, GBR and Control groups at enrolment (4.54mm to 5mm), with the baseline measurements comparable to the incisors keratinised measurements of 4.5 – 5mm recorded by Lang and Loe (1972) in the maxillary arch. Whilst the canine and premolar dentition can record a lower buccal gingival height of 2.5- 3.5 mm (Abt et al., 2012), both the SS and Control groups included two premolar teeth, with the GBR group containing one canine and one premolar. This equal distribution of non-incisor dentition reduced the risk of bias from an unequal distribution of dissimilar teeth.

The findings from this study appears to suggest that whilst GBR was superior to the SS technique, when the KT width is review after 4 months healing, the difference would not be clinical advantageous when compared to unassisted healing. This conclusion was also observed by Festa et al., (2013), who reported on the gingival tissue height following socket grafting, using a combination of porcine xenograft and cortical membrane, and Iasella et al., (2003), who examined the effect of GBR using a collagen membrane and allograft material. Both studies indicated either no change or a small loss (0.1mm) in the keratinised tissue dimensions in SS or GBR groups at implant placement.

8.8 Conclusion

At 4 months, a SS technique using a Mucograft® coronal seal, offered no advantage in mid-buccal vertical contour height when compared to the Control. The loss of horizontal contour and the thinning of the gingival tissue associated with SS ARP, has the potential to affect implant surgical implant protocols and aesthetic outcomes. GBR ARP was observed to more effective at preserving vertical and horizontal tissue contour and gingival dimensions.

Chapter 9

Histological Assessment of Alveolar Bone Healing Following ARP
Material And Method

9.1 Introduction

The healing and re-organisation of the alveolar socket following tooth extraction, is a complex and multi-factorial process (Jung et al., 2018, Tonetti et al., 2019) Several distinctive phases of the healing process have been identified, with the initial trauma leading to clot formation, primary gingival and alveolar remodelling and long-term alveolar reconfiguration. Healing at the wound site is characterised by re-organisation, proliferation and maturation of the local oral tissue, causing dimensional, volumetric and histological changes to the alveolar bone and gingival tissue (Araujo et al., 2015).

The bone and soft tissue remodelling process is influenced by host and tooth extraction site factors. These include the patient's medical status, the presence of local infection, previous periodontal disease, traumatic injury and the presence of, or thickness of the alveolus at the tooth extraction site (Garg and Guez, 2011, Araujo et al., 2015).

The accumulative effect of these changes leads to a significant and progressive modelling and remodelling of the alveolar ridge (Chappuis et al., 2017, Hansson and Halldin, 2012). These processes cause local changes to the composition of the compact and cancellous bone (Ulm et al., 1992), a reduction in local bone density (Ulm et al., 1992, Reich et al., 2011) and alteration to the height, width and three-dimensional morphology of the site (Schropp et al., 2003b, Araujo and Lindhe, 2005, Bartee, 2001, Atwood, 1971). Further remodelling of the healed residual ridge can occur as a result of anatomical, prosthetic, metabolic and functional factors (Atwood, 1979, Atwood, 1971), with the remodelling process recorded as continuing throughout life (Sculean et al., 2019).

Although ARP techniques have been described as being able to maintain the tissue contours in extraction sites, the quantity of the replacement bone tissue has been found to be variable (Vignoletti et al., 2012, Horváth et al., 2013, Vittorini Orgeas et al., 2013). Differences have been found in the histological bone composition between individuals, ARP techniques and the healing period since tooth extraction. Further research is now needed to explain the differences in bone healing patterns between GBR and SS ARP techniques (Postlethwaite et al., 1978, Cardaropoli et al., 2014). The present study compares the histological composition of harvested alveolar bone biopsies, after 4 months healing, following ARP using a GBR or SS techniques. Unassisted healing acted as the Control. Bone samples were collected at Type-3 implant placement.

9.2 Study population

Forty-two patients were split into 3 groups (n=14 per group) as following: Group 1(test): Guided Bone Regeneration (GBR), using a combination of deproteinized bovine bone mineral (DBBM) and a porcine

collagen membrane/barrier: Group 2 (test). A Socket Seal technique combining the use of DBBM and a porcine collagen matrix: Group 3 (Control). Unassisted socket healing. Forty-Two samples underwent Back Scatter Electron Scanning Electron Microscopy (BSE-SEM) imaging, with fifteen samples analysed using Xray Micro-Tomography (XMT). In the XMT imaging group, six sample were included from the GBR and SS test groups, with three samples included from the Control.

9.3 Harvesting of bone sample

A 0.2% chlorhexidine rinse was administered before treatment, with Paracetamol 500mg prescribed for post-operative pain control.

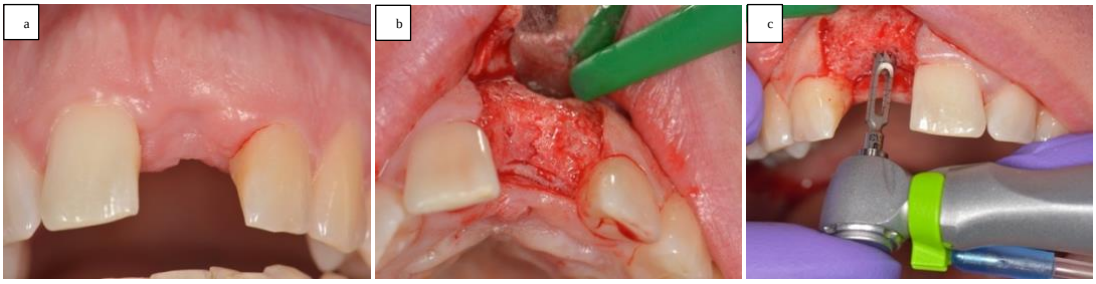


Figure 33. *Harvesting of bone core. (a) Healed socket area (b) Full thickness mucoperiosteal flap raised to expose the alveolar ridge. (c) 21 healed extraction site, with trephine being used to harvest bone sample.*

A horizontal incision was undertaken on the crest of the alveolar ridge, extending the full length of the edentulous space. Two vertical relieving incisions were then placed on the mesial aspect of the adjacent dentition, extending vertically into the free gingival margin. These incisions allowed a full thickness mucoperiosteal flap to be raised, to expose the buccal and palatal aspect of the alveolar process of the healed extraction site. A surgical trephine (STOMA, Germany) with an external diameter of 3mm and an internal diameter of 2mm, was then used to harvest a bone sample (*Fig. 34*). A custom surgical stent was utilised to aid the orientation of the trephine according to a prosthetically driven protocol. A bone core of at least 7mm length was collected and stored in a storage jar containing 70% ethanol, before laboratory analysis. Further preparation of the site was undertaken according to a Nobel Parallel implant surgical protocol, prior to implant fixture placement (NobelBiocare, 2014).

9.4 Polymethylmethacrylate embedding of bone

At the laboratory, the bone samples were placed in 100% ethanol for 2 over days, before being transferred into a solution of xylene. After 2 days, the bone samples were then relocated to a jar

containing uncatalysed methyl-methacrylate monomer and after a further 3 days, moved into a glass specimen pot containing a polymerising mixture of Poly (Methyl-Methacrylate) (PMMA). The PMMA solution was allowed to partially set, before being placed into an oven at 35°C, until it had a firm consistency. The temperature in the oven was then increased to 45°C, to promote final hardening of the PMMA. The outer glass pot was then removed, with the surplus PMMA sectioned using a band saw to orientate the examination surface of the block. The orientation of the block was configured, to create a bone surface suitable for BSE-SEM examination, with coronal and apical areas of the sample marked. A specimen ID number was then scored on the body of the PMMA block using a diamond scribe. The surfaces of the block were polished using grades of carborundum paper wheels under continuous cold-water lubrication (1200 grit paper). The examination area was polished using 2400 and then 4000 grit papers, with the polishing paper supported on a clean, flat glass plate. The block was rinsed in distilled water in an ultrasonic bath between stages, to remove any displaced polishing abrasive from the grit paper. The surface was blotted dry and checked under a dissecting microscope and imaged using BSE-SEM (Fig. 35).

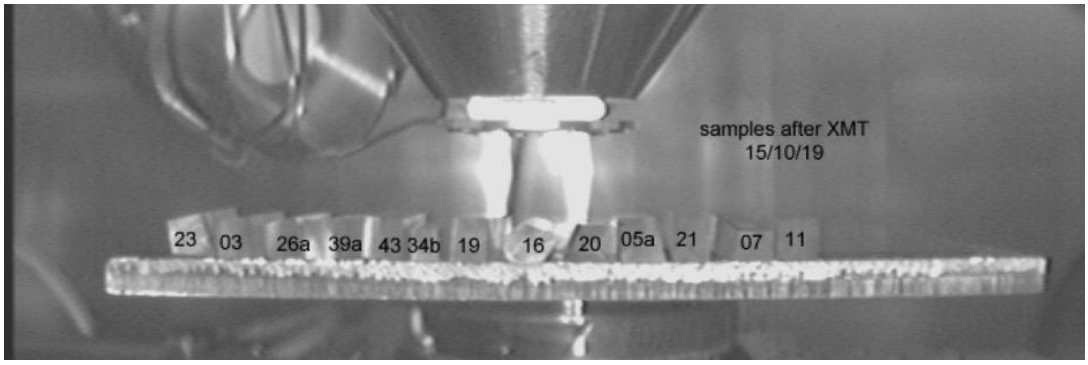


Figure 34. *Prepared PMMA embedded bone samples prior to BSE-SEM imaging.*

9.5 Iodine sublimation

An Iodine sublimation staining process was used to enhance the information contained in the BSE-SEM images (Ley et al., 2014 and Boyde et al., 2014*)*, as it allowed for visualisation of the tissue phases in the sample, including osteoid, cell structures and connective tissue matrix (Boyde, 2012).

Iodine sublimation was undertaken by placing the polished PMMA blocks in a sealed 10 cm diameter glass jar. Iodine crystals of (~ 0.2 grams) were then placed in a separate glass pot in the same jar, with the larger jar lid firmly screwed down. The samples were left in the glass jar for a week and then removed and examine by BSE-SEM. The progress was monitored qualitatively by observation the brown colour change in the specimen over the course of the 7 days. Following completion of the procedure, the Iodine can remain labile and can resublime out of the sample. To prevent this from

happening, a separate glass container was used to store the specimen's following completion of the sublimation process.

9.6 Histological image analysis

Qualitative assessment of the histological composition of the embedded bone specimen was undertaken using images created by the BSE-SEM and XMT (MuCAT Scanner) systems. The XMT images were recorded after BSE-SEM examination, as it allowed for the cut PMMA block surface to be compared and matched in both imaging modalities. XMT analysis also allowed the bone sample to remain intact, whilst analysing the complete 3D bone volume. The process also facilitated visualisation of the bone sample in any plane, by 're-sectioning" of the data (*Fig. 36* and *Fig. 37*).

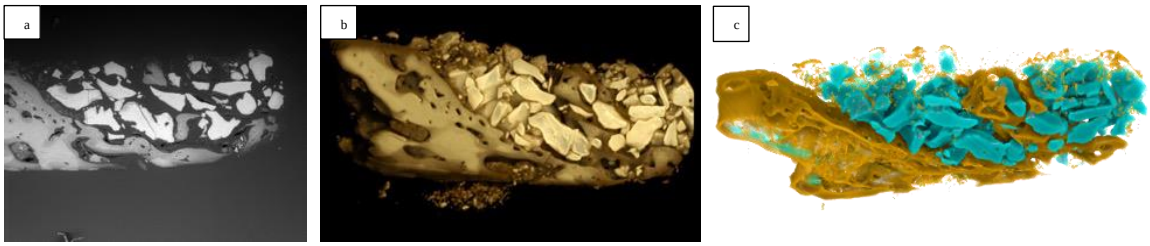


***Figure* 35.** *Comparison of BSE-Sem and XMT images for a SS bone core sample (a), BSE-SEM (b) XMT image and (c) Volume rendering images of the bone core sample presented in a 2D format.*

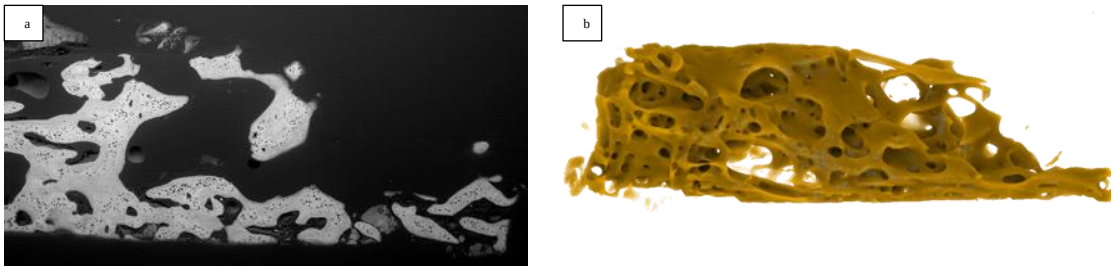


Figure 36. *Comparison of BSE-SEM and XMT volume rendering images of new alveolar bone formation in an un-assisted healing bone core sample. (a) BSE-SEM image. (b) XMT 3D volume rendering image presented in a 2D format.*

9.7 Analysis of BSE-SEM images

A Tagged Information File Format (TIFF) image was saved following BSE-SEM imaging of the embedded bone sample. This image was then imported into the Image-J software programme (Image J 1.52a, National Institute of Health, USA). Delineation of the core sample was undertaken using the polygon tool, with the unselected part of the image deleted, using the clear background function. Two duplicate TIFF files were then saved. The original TIFF image was used as a baseline for comparative analysis, following image transformation functions. The duplicate images were analysed to determine the percentage of residual graft and new bone formation in the core sample.

In the first duplicate image, DBBM particles were identified and individually selected using the polygon outline function. The particles were then sequentially added to the overall image selection area, through the addition function, coloured with a red infill and the image saved (Doube et al., 2010).

The same process was repeated to record the presence of alveolar bone, with the selected bone particles coloured with a blue infill. Bone and graft debris, produced during the trephination and embedding of the bone samples, was excluded from the selection process. The accuracy of the DBBM and trabecular bone selections was reviewed by overlaying the selected bone and DBBM sections onto the original SEM at a 50% translucency. Fusion of the DBBM and trabecular bone images was then undertaken, to create the final image used for histological quantitative analysis

The RGB function in the threshold tool, was used to separate the blue and red coloured components of the combine DBBM and alveolar/trabecular bone image, with a separate percentage for each selection recorded using the Outline Particle function (*Fig. 38*).

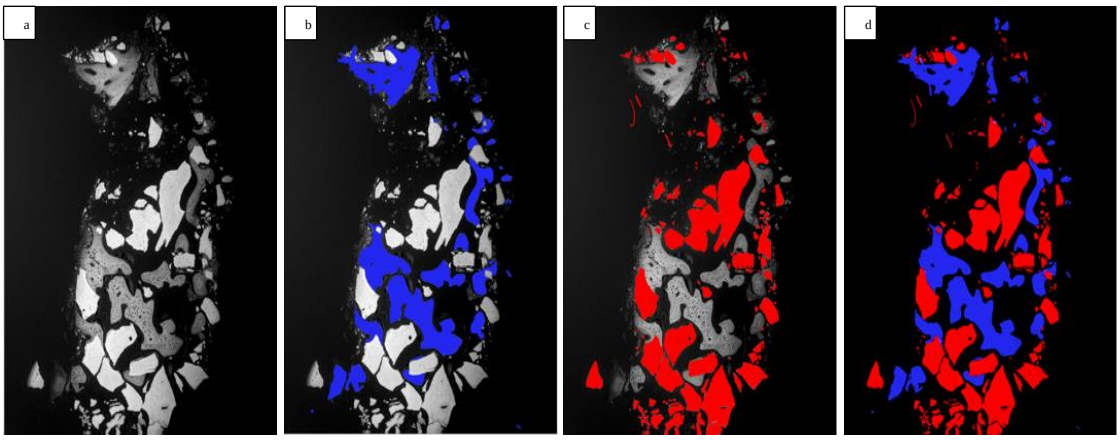


Figure 37. *Image analysis of BSE-SEM bone and graft composition. (a) Original TIFF image. (b) Bone selected and infilled with Blue. (c) DBBM selected and coloured in red. (d) Merged image for histomorphometric analysis.*

9.8 XMT micro-CT images

Image J and a custom Interactive Data Language (IDL) programme (Harris Geospatial Solutions) was used to calculate the percentages of new bone, residual graft particles and connective tissue in the XMT image files. Whilst BSE-SEM images are restricted to the analysis of the bone samples in a single plane, the examination of multiple XMT image slices at 7-20 microns magnitude and tomography referencing of Nucleoside distance transformations, allowed for examination of the complete 3D volume. The process also facilitated visualisation of the 3D data set in any plane by 're-sectioning" of the data.

9.9 Bone core volume analysis

An initial grey-level threshold of 1.0 was set, as it was approximately half the grey-level of bone. Using the Euclidean distance transform (EDT), an outer boundary was defined 0.5 mm outside all voxels with grey levels above this threshold. A region-growing algorithm (Pohle and Tonnies, 2001) where all voxels outside this boundary were selected, prevented large, enclosed voids in the sample from being counted as outside. Using the EDT, an inner boundary was defined 0.6 mm inside these selected voxels.

This new boundary was therefore 0.1 mm inside the sample edge and ensured that any image analysis was calculated with the boundary of a bone or graft particle and only voxels within this boundary were selected for analysis.

9.10 Segmentation of histological particles

The magnitude of the grey-level gradient was calculated for every voxel using the central difference theorem. Three threshold levels were selected by the user, to represent bone, graft and connective tissue. A mid-threshold was also defined and was calculated at halfway between the identified bone-threshold and the graft-threshold. A voxel in the sample was defined to be graft, if its grey-level is above the connective tissue-threshold, or if its grey-level was above the mid-threshold and its gradient was above the connective tissue-threshold. A voxel was defined to be within bone if its grey-level was between the bone-threshold and graft-threshold and its gradient is less than the connective tissue-threshold. This approach eliminates errors where voxels near the boundary of graft and connective tissue/embedding material have a grey-level similar to that of bone (reference). The user was able to adjust the thresholds, whilst visualising the segmented volume, to allow an independent element of adjustment. The external parameters of the bone core were taken within the identified bone edge, to avoid edge effects and an over estimation in size. The volume selected was then shrink-wrapped to measure compositional volume.

9.11 Calculation of graft, bone and osseointegration percentage

Using the EDT transformation, the distance from voxels outside bone to the defined bone surface was calculated, with the distance from all voxels within the graft to the graft surface also determined.

The graft edge was defined as all voxels that are less than two voxel-dimensions inside the graft surface and whose gradient is greater than half the threshold-gradient. The bone edge was defined as all voxels that are less than two voxel-dimensions outside the bone surface and whose gradient is greater than half the threshold-gradient. Osseointegrated voxels were considered to be those that appear in both the internal graft edge and external bone edge. The percentage of osseointegration was an expression of the ratio of osseointegrated voxels to graft-edge voxels (*Fig. 39*).

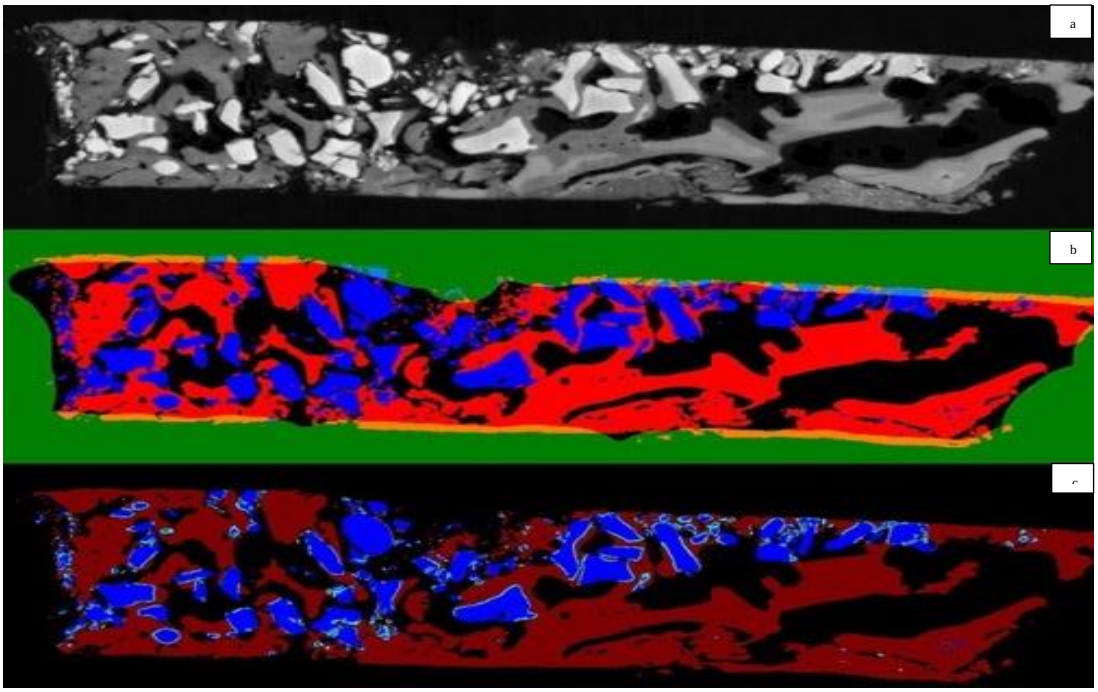


Figure 38. *XMT image analysis using the IDL computer programme. (a) Original XMT image. (b) Shrink-rapped particle measuring sample volume. (c) Percentage of osseointegration recorded (light blue line, surrounding dark blue DBBM particles.*

9.12 Visualisation of graft, bone and matrix

Drishti (Drishti v2.6.3, Australian National University), a cross-platform open-source volume rendering programme, was used to render saved Tomography (TOM) XMT files into a 3D volume rendering image for visual examination (*Fig. 40*

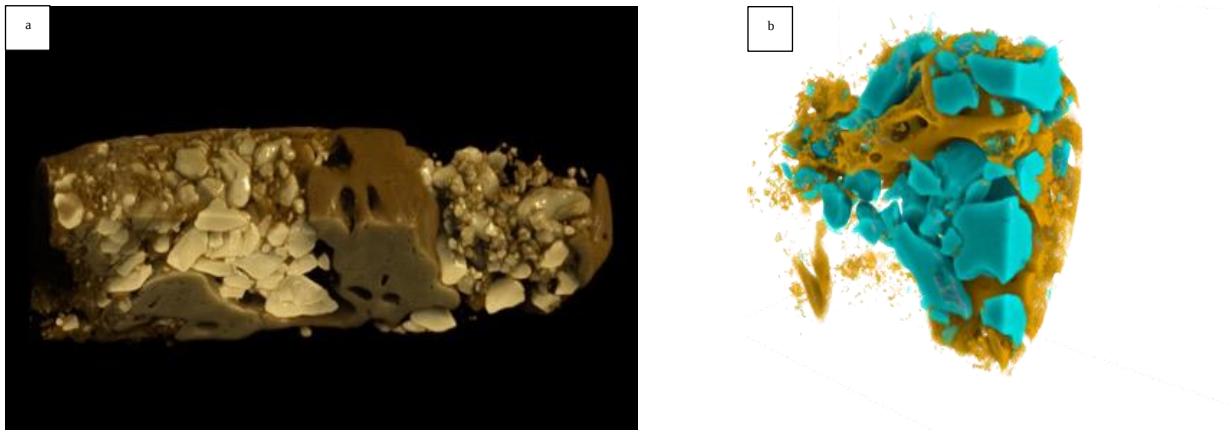


Figure 39. *XMT images demonstrating alveolar and DBBM composition. Images (a) and (b) demonstrates a bone core sample where GBR has been undertaken and where the integrated DBBM and alveolar bone particles have formed bone bridges through the gaps in the DBBM particles. Both images are a 3D volume presented in a 2D format.*

9.13 Examination of DBBM particles following socket healing

Unused DBBM particles were placed on a mounting platform or alternatively embedded in PMMA blocks and prepared in a similar manner to the ARP test samples. BSE-SEM imaging of the new DBBM particles was undertaken to determine whether visual evidence of ongoing osteoclastic or osteoblastic cellular activity was observed on the residual graft particles following 4 months healing.

Isolated areas of both the newly embedded DBBM particles and the original GBR and SS prepared cores, were etched with a 15% hydrochloric acid etch (DMG Icon etch), using a tiny drop applied to the end of an applicator syringe (DMG Dental). The etch time was restricted to 5 minutes, to allow sufficient time for the dissolution of the surface bone mineral tissue and a component of the organic matrix. This period was considered sufficient to allow dissolution of the top mineralised surface, exposing the most superficial osteocyte lacunae if present. The acid etching process was then stopped by the addition of 7% available chlorine hypochlorite bleach, which was washed off with distilled water and the sample blot dried. The surface then underwent BSE-SEM imaging, with the exposed acrylic surface examined to investigate the external and internal morphology of the calcified bone and DBBM particles.

9.14 Sample size calculation

The power calculation for this RCT was based on the primary outcome measure of vertical radiographic dimensional change described in Chapter 5, section 9. Despite this, statistical analysis based on the number of patients included from the primary outcome, would be sufficient to identify statistical significance of this secondary outcome. This is because assuming an ARP vital bone formation of 39.6% +/- 9.4, and an unassisted control mean of 29.5% (Crespi et al., 2011b), then a three grouped study would require a sample size of 14 to produce an 80% power at an alpha level of 5%.

19.15 Statistical analysis and randomisation

All data was entered in a computer database, proofed for entry errors and loaded in the SPSS statistical software package (v.22). Trabecular bone, bone graft and connective tissue percentages were recorded as a mean ± standard deviation for the GBR, SS and Control bone samples. To examine the working hypothesis and determine whether a statistical difference was present between the bone and connective tissue composition of the three test groups, significance was set at $p < 0.05$, with differences between groups assessed using a parametric method as the results were noted to be normally distributed (Shapiro Wilk Test) and had approximately equal variances (Levene's test of Variance). Independent samples t-tests were used to examine the differences in means between groups, with a One-way fixed effect ANOVA and Tukey's HSD used to test variance.

Analysis of the BSE-SEM images was repeated at 2-weeks, to determine the percentage of new bone formation and residual DBBM particles in the test images. An intra-class correlation coefficient was used to measure the level of intra rater reliability for bone and graft composition from 40 repeat histomorphometry measurements.

Chapter 10

Histological Assessment of Alveolar Bone Healing Following ARP
Results and Discussion

10.1 BSE-SEM quantitative assessment of new bone formation (%)

At 4 months healing, analysis of the trephined bone samples indicated significant variation in the histomorphometric characteristics of the bone specimens. The percentage of new trabecular bone formation was markedly higher in the Control (45.89% +/- 11.48), when compared to both the GBR (22.12% +/- 12.7) and SS (27.62% +/- 17.76) groups. The newly formed bone tissue was predominately seen in the apical and middle third of the healed socket in the GBR and SS samples, only extending to the coronal area in five GBR and one SS case (*Fig. 42 and 43*). Less bone was found coronally in the control group, due to incomplete regeneration of the socket and variation in the coronal morphology of the sample.

The presence of new bone formation was completely absent in the coronal and middle section of the bone sample in one SS case where the occluding matrix was lost, and in two further SS cases when early dehiscence of the matrix had occurred at days 6-8. Coronal bone was absent, with a significant reduction in mid-socket new bone formation, when partial break down of the occluding barrier or matrix occurred in three GBR cases and four SS cases respectively.

ANOVA analysis demonstrated a statistical difference in the percentage new bone formation, when comparing the GBR and Control (P=0.004), and the SS and the Control groups (P=0.005). No statistical difference was found when relating GBR and SS bone formation. The percentage of connective tissue was observed to be similar in both the GBR (49.72 % +/- 9), SS (47.81% +/- 12.57) and Control (47.81% +/- 12.57) test groups. Following ARP, the level of residual DBBM graft was comparable when using a GBR (28.17% +/- 16.64) or SS (24.37% +/- 18.61) procedure (Table 34).

The intra-class correlation co-efficient demonstrated a measurement reliability of 0.88 (CI 0.83 to 0.94) when examining bone and graft percentage values.

Table 34. *Mean Bone, Residual Graft and Osseointegration Volume, following BSE-SEM Qualitative Analysis (%)*

	CONNECTIVE TISSUE			BONE			GRAFT	
Patient Number	SS	GBR	CONTROL	SS	GBR	CONTROL	SS	GBR
1	48.38	50.11	73.12	31.64	3.58	26.88	19.98	46.31
2	39.67	46.75	42.99	24.87	23.13	57.01	35.46	30.12
3	34.1	36.36	65.14	49.84	41.76	34.86	16.06	21.88
4	45.45	39.62	58.32	14.3	2.36	41.68	40.25	58.02
5	33.61	63.71	43.93	35.02	33.07	56.07	31.37	3.22
6	33.22	58.78	52.47	7.43	20.12	47.53	59.35	21.1
7	32.14	33.03	38.86	64.51	20.46	62.14	3.35	46.51
8	63.4	57.63	48.29	34.6	27.17	51.71	1.3	15.2
9	47.55	46	61.5	13.1	20.72	38.5	39.35	33.28
10	73.5	57.21	46.52	20.35	33.87	53.48	6.15	8.92
11	49.19	47.36	40.99	6.69	21.64	59.01	42.12	31
12	56.37	50.17	72.36	39.58	2.6	27.64	4.02	47.23
13	58.5	51.28	51.95	4.6	39.32	48.05	36.9	9.4
14	54.27	58.01	62.07	40.15	19.89	37.93	5.58	22.14
Mean SD	47.81 SD 12.57	49.72 SD 9	54.18 SD 11.38	27.62 SD 17.76	22.12 SD 12.7	45.89 SD 11.48	24.37 SD 18.61	28.17 SD 16.64
One-way ANOVA	0.30			<0.001			0.57	
F Test	1.22			10.69			0.323	
Tukey's HSD (p) 0.05				SS Vs. Control p=0.04 GBR Vs. Control p=0.002				
Loss of Membrane Partial Membrane breakdown								

10.2 XMT quantitative assessment of percentage bone and graft volume

Analysis of the XMT bone 3D images, indicated a comparable but slightly lower level of bone and residual DBBM graft volume, when the percentage XMT volumes were compared with the area measurements taken from the BSE-SEM images The amount of new bone formation seen in the XMT images was again higher in the Control (44.43% +/- 6.38) group, with the GBR (21.27% +/- 13.82) and SS (19.83% +/- 22.13) techniques having a lower level of new bone formation (Table 35). New bone formation in the coronal aspect of the socket in the control was incomplete and reduced in outline, when compared to the GBR and SS groups.

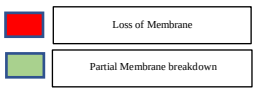
The volume of residual graft matrix was greater with GBR (25.41% +/- 12.11), when compared to SS (18.29% +/- 11.14), with the level of osseointegration between the graft particles and bone, higher with

GBR (35.66 +/- 9.8) when equated to SS (31.18 +/- 19.38). New bone formation was almost absent in the three SS case which experienced loss of the membrane and was reduced in the three GBR bone samples which were noted to have suffered flap breakdown or dehiscence. One SS change which lost the membrane and suffered extensive graft sequestration during the early stages of healing, demonstrated similar healing characteristics to the Control.

ANOVA analysis found no statistical difference in the percentage volume of newly formed bone, residual graft matrix and osseointegration levels when comparing the GBR and SS ARP test groups.

Table 35. *Mean Bone, Residual Graft and Osseointegration volume, following XMT Qualitative Analysis (%)*

SAMPLE	Bone			Graft		Integration	
	SS	**GBR**	**Control**	**SS**	**GBR**	**SS**	**GBR**
1	3.00	3.00	40.80	22.10	27.00	24.50	24.00
2	3.70	35.40	51.80	27.00	12.70	23.30	31.70
3	53.2	36.70	40.70	7.80	19.50	59.50	42.90
4	42.80	16.00		14.90	49.00	56.80	53.00
5	31.50	22.90		0.20	18.00	28.41	31.00
6	3.42	4.90		30.90	31.70	10.63	29.00
7	1.20	30.00		25.12	20.00	15.13	38.00
Mean	19.83	21.27	44.43	18.29	25.41	31.18	35.66
SD	22.13	13.82	6.38	11.14	12.11	19.38	9.80
One-way ANOVA	0.129			0.274		0.59	
F Test	2.38			1.31		0.29	
Tukey's HSD (p) 0.05							
Percentage (%) are representative of the histological volume of each tissue constituent in the whole trephined sample							



10.3 Qualitative BSE-SEM and XMT bone particle analysis

The BSE-SEM and XMT images demonstrated that in terms of bone quality, comprehensive alveolar socket healing had occurred in the Control group, with osteogenesis of new bone and extensive lamellar bone formation recorded in the socket at 4 months healing. However, the pattern of healing in the Control biopsies indicated a higher level of connective tissue coronally, with incomplete bone formation/regeneration of the socket on the buccal aspect. The bone healing in the coronal area of the socket was incomplete, with connective tissue seen to extended into the mid-socket area.

The pattern/features of the bone regeneration in the GBR and SS test groups were different to the Control, with less new bone formation in the mid socket area and evidence of extensive fibrous encapsulation of the graft matrix in the coronal area. The GBR technique was able to demonstrate localised areas of new bone formation in the coronal area, with a similar level of bone formation rarely seen with the SS technique. Extensive fibrous encapsulation of the DBBM graft was observed with both GBR and SS groups when early breakdown or dehiscence of the membrane or matrix occurred. When early breakdown of the SS collagen matrix was reported, the bone biopsy was seen to be nearly completely composed of fibrous encapsulated graft matrix (*Fig. 41, 42, 43 and 44*).

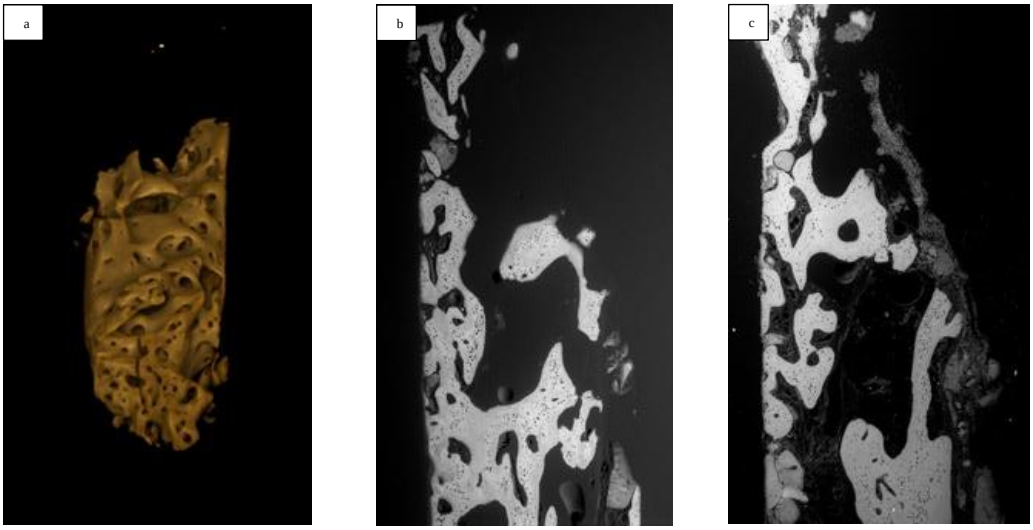


Figure 40. *XMT, BSE-SEM and Iodine imbued images of unassisted healing group. (a) XMT 3D volume rendering image of healed alveolar bone. (b) BSE-SEM images of the same GBR sample demonstrating remodelling lamella bone. (c) Iodine staining of the BSE-SEM images demonstrating connective tissue matrix, blood vesicles and cellular characteristic*

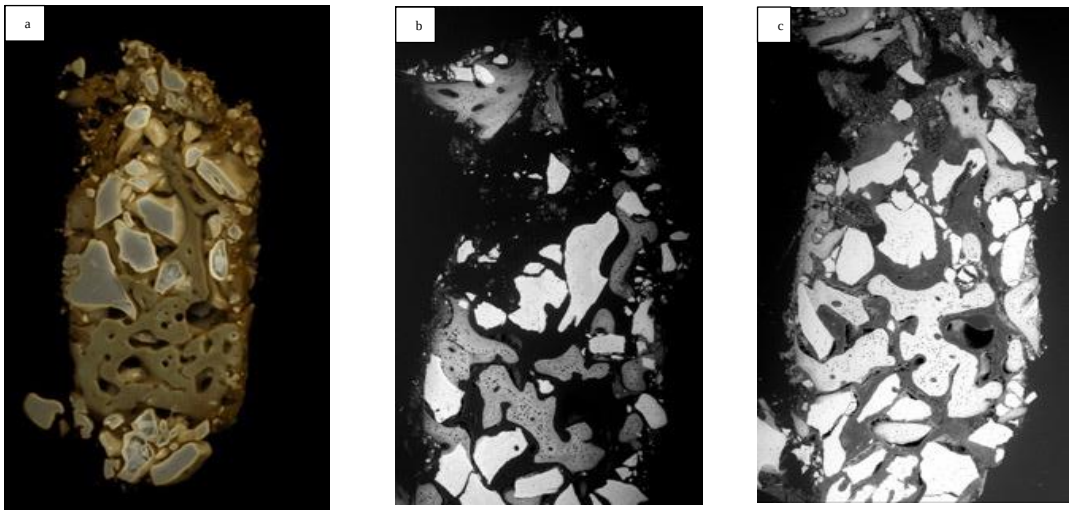


Figure 41. *BSE*-SEM and *XMT images of a GBR core. (a) XMT 3D volume rendering image of healed alveolar bone, demonstrating new alveolar bone formation, osseointegration of graft particles and fibrous encapsulation of the coronal particles. (b) BSE-SEM images of the same GBR core demonstrating remodelling lamella bone, but with a loose graft/fibrous matrix coronally. (c) Iodine staining of the BSE-SEM images demonstrating connective tissue matrix, blood vessels and fibrous encapsulation of the graft coronally.*

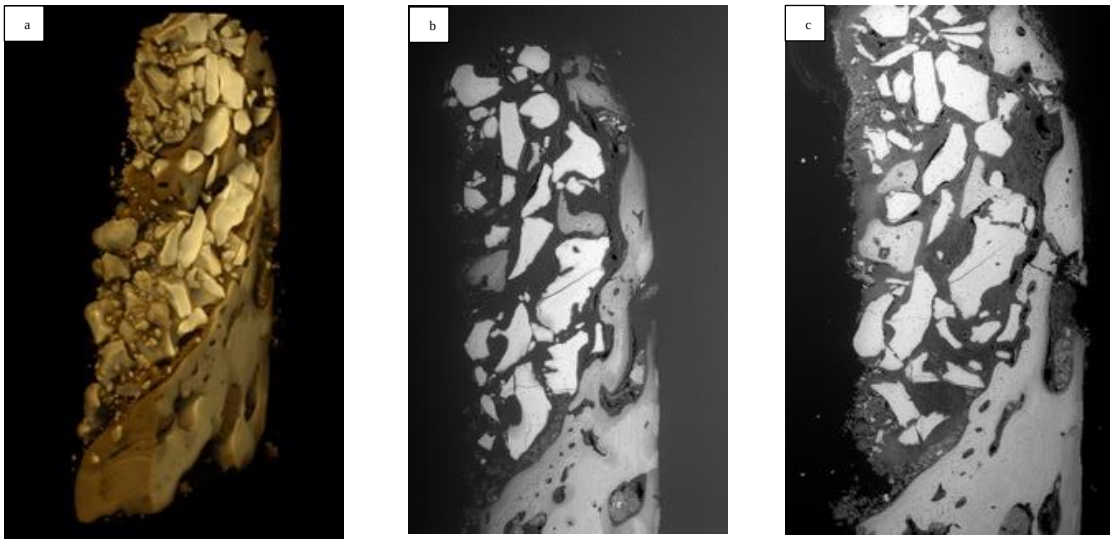


Figure 42. *BSE*-SEM and *XMT images of a SS core. (a) XMT 3D volume rendering image of healed alveolar bone, demonstrating new alveolar bone formation, but less osseointegration of graft particles. An irregular graft matrix is seen coronally. (b) BSE-SEM images of the same SS core demonstrating apical alveolar bone remodelling, lamella bone, but a loose graft/fibrous matrix coronally. (c) Iodine staining of the BSE-SEM images demonstrating connective tissue matrix and extensive mid and coronal fibrous encapsulation of the graft matrix.*

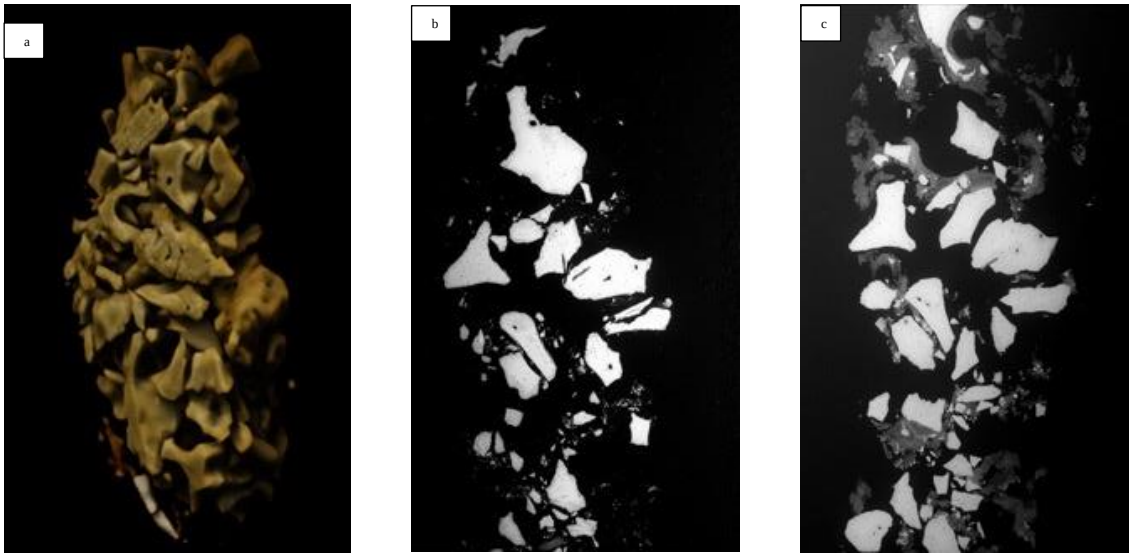


Figure 43. *BSE-SEM and XMT images of a SS core, where early loss of the occluding membrane was recorded. (a) XMT 3D volume rendering image of trephine bone, demonstrating no new alveolar bone formation. (b) BSE-SEM images of the same SS core demonstrating a loose graft matrix filling the entire core. (c) Iodine staining of the BSE-SEM images demonstrating connective tissue matrix, and fibrous encapsulation of the entire trephined core.*

New bone formation in the GBR and SS groups was mostly observed in the mid and apical areas of the healed socket. Eleven GBR and seven SS cases had visible evidence of new bone-DBBM graft osseointegration on BSE-SEM images. The features of the osseointegration included the development of linked bone bridges between the newly formed bone and graft particles, or total bone encapsulation of the graft (*Fig. 45*). When a void had been created in the socket during placement of the ARP DBBM graft, four GBR and three SS cases demonstrate new bone formation in the remaining spaces.

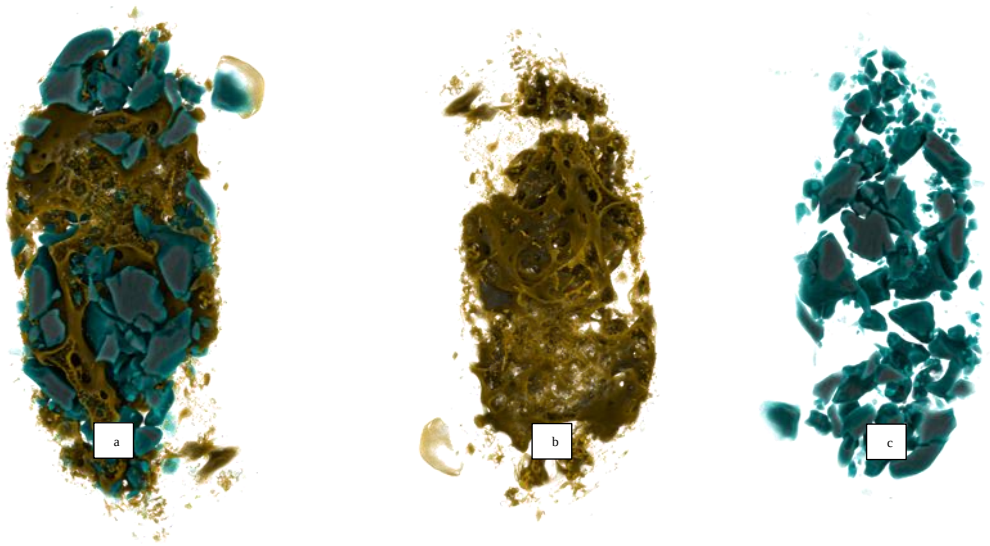


Figure 44. *XMT 3D volume rendering image demonstrating how the alveolar bone has regenerated in the residual spaces in the xenograft matrix, following GBR. (a) Composite image of bone and xenograft. (b) 3D bone volume presented in a 2D image. (c) Xenograft 3D volume presented in a 2D image.*

The iodine sublimation process suggested significant fibrous tissue encasement of the DBBM graft particles in both the GBR and SS cases in the coronal area of the socket (Boyde, 2012). No evidence of widespread osteoblastic cellular remodelling of the graft particles was noted in these samples. Examination of the decalcified inverted PMMA architecture of the GBR and SS samples, indicated that the residual graft particles still retained the same anatomical features as the original DBBM particles. Whilst evidence of osteoblastic remodelling was observed on the unused and residual graft particles, the surface appearance of the graft had not appeared to change, suggestive of a lack of further physiological resorption. The widespread cellular and topographical appearance of the actively remodelling bone tissue was not replicated on the graft particles, again suggestive that no active remodelling of the DBBM particle was present (Fig. 46, 47, 48 and 49).

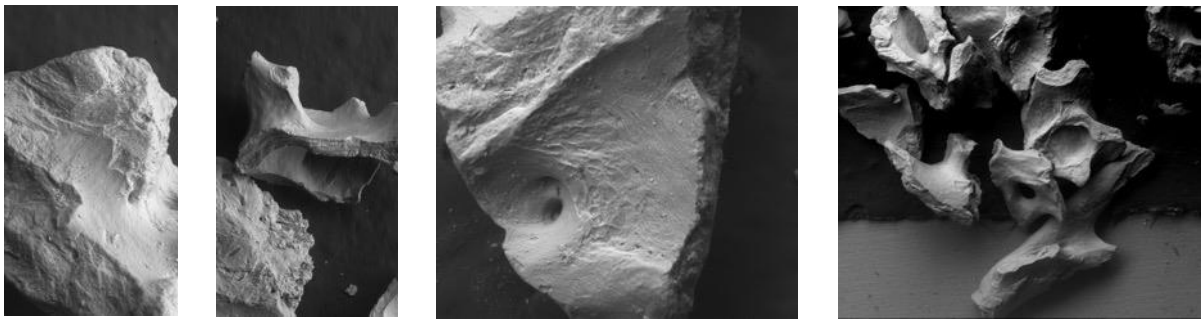


Figure 45. *Four images of unused DBBM graft particles, demonstrating surface osteoblastic and osteoclastic remodelling.*

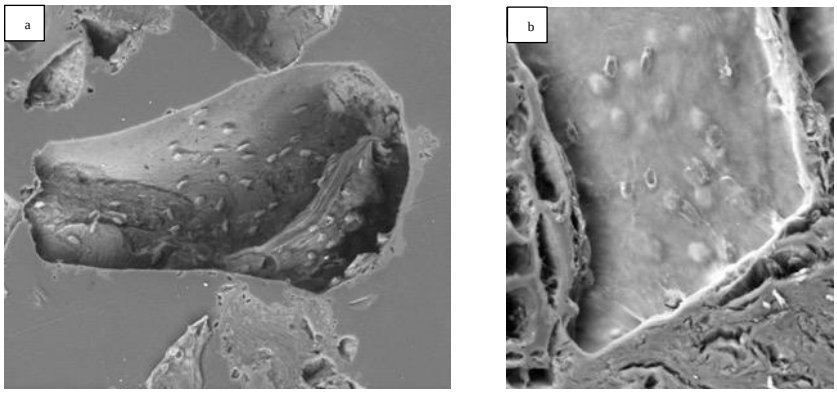


Figure 46. *Two images of unused DBBM graft particles, embedded in PMMA, following acid dissolution. The two images (a) and (b) demonstrate surface osteocyte lacunae on the surface of the bone, suggestive of osteoclastic remodelling of the original bone prior to medical preparation.*

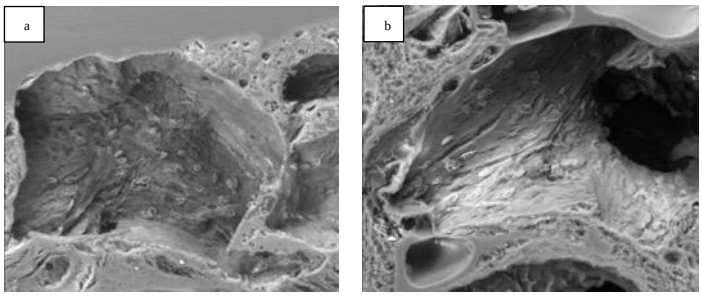


Figure 47. *BSE-SEM images of SS core sample, following acid dissolution of the surface of the sample. Images (a) and (b) demonstrate no change to the surface osteocyte lacunae indentations on the surface of the bone, suggestive of no additional osteoclastic remodelling.*

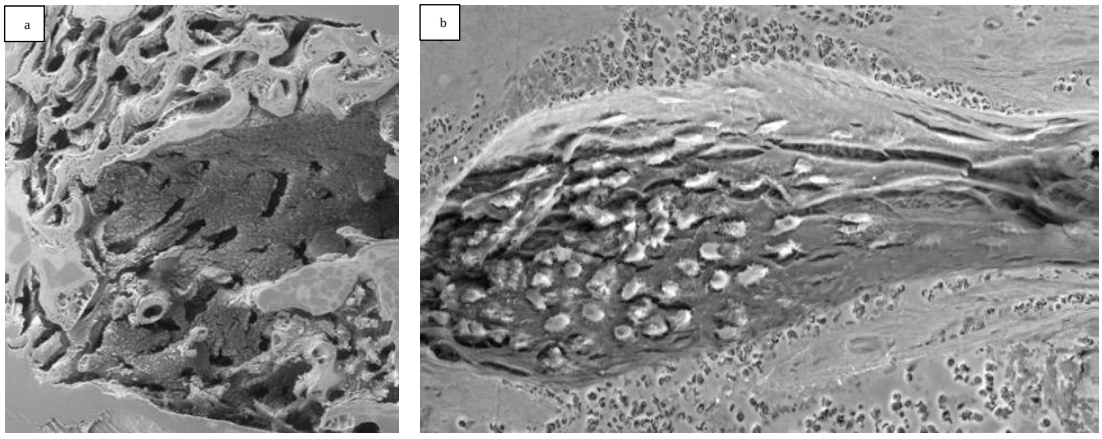


Figure 48. *BSE-SEM images of unassisted healing core, following acid dissolution of the surface of the sample. Images (a) and (b) demonstrate a significant number of osteocyte lacunae indentations on the surface of the bone, suggestive of extensive additional osteoclastic remodelling.*

20.4 Discussion

Tooth extraction results in direct damage to the alveolar bone process and supporting periodontium, rupturing the blood vessels and causing separation of the periosteum and connective tissue attachment. Consolidation and reorganisation of the fibrin clot, leads to the formation of a collagen provisional matrix, with this granulation tissue containing blood vessels, fibroblasts, and chronic inflammatory cells (Hammerle et al., 2012a). The ensuing sequence of bone healing, modelling and remodelling is complex and can be considered with regards to proliferation and maturation of the bone through a regenerative and reparative process, with the healing mechanism considered as intramembranous ossification (Sculean et al., 2019).

ARP techniques have been advocated to promoting favourable healing of the alveolar ridge (Barone et al., 2008, Cardaropoli and Cardaropoli, 2008), as the procedures have been observed to facilitate physiologically repair and cellular regeneration, ensuring a stable or augmented bone foundation prior to implant placement (Horváth et al., 2013, Darby et al., 2008, Wang et al., 2004). Whilst the GBR and SS ARP techniques are associated with a unique surgical protocol, the use of a xenograft matrix and placement of a specific collagen graft / barrier material, they share several features. They provide a matrix for mechanical support, compartmentalising the alveolar bone and gingival tissue to promote tissue regeneration (Gottlow et al., 1986), provide a mineral reservoir which promotes the induction of new bone formation (Kumar et al., 2013) and rely on the availability and cellular activity of odontogenic cells derived from the socket wall site to encourage osteoconduction and bone modelling and remodelling (Sculean et al., 2019).

10.4.1 ARP GBR and SS socket healing

This study is the first to use BSE-SEM and XMT image analysis, to calculate the histomorphometric bone composition in the healed extraction socket. Quantitative analysis of the GBR technique, demonstrated conformity between the percentage new bone area (22.12%) and bone volume (21.27%), with this study being the first to compare bone and area measurement. The percentage of new bone in the test sample was similar to the histological outcomes recorded by Barone et al. (2008), where he indicated 25.7% of new bone and 51.1% of connective tissue formation when using a GBR technique. Cardaropoli et al. (2012) recorded a higher level of new bone (43.82%) and a lower level of connective tissue (43%) development, with the GBR ARP technique in general, more regularly characterised by a higher percentage of connective tissue and residual graft, with a smaller percentage of newly formed bone (Carmagnola et al., 2003, Araujo and Lindhe, 2009, Araújo et al., 2010). This reduction in new bone formation was reported in the systematic review undertaken by Chan et al. (2013), who indicated that DBBM ARP techniques resulted in a range of -22.2% (decrease) to 9.8% (increase) in new bone formation. This variability in the results may be attributed to differences in the sample biopsy and 2D image preparation. Volumetric assessment of bone biopsies is considered to be a more accurate and representative measurement of the healed bone composition and provides greater insight into the true healing characteristics of the socket area.

The advantage and discernment offered when using XMT image volumetric analysis, was again observed when evaluating the bone healing pattern following SS ARP techniques. Differences were recorded in the area and volume quantitative measurements, with a higher area of new bone and residual graft and a lower area of connective tissue noted with 2D BSE-SEM imaging, when compared to XMT volumetric analysis. Lindhe et al. (2014) conducted a histological examination of bone healing, following SS ARP with a DBBM graft and a porcine collagen plug, indicated that the amount of bone marrow and osteoid tissue was five times greater in the unassisted healing site, when compared to the SS grafted socket. The SS biopsy was composed of 39.9% (+/- 8.6) new bone matrix, 32.4% (+/- 9.2) fibrous tissue and 19.0% (+/- 6.5) residual graft matrix. Lindhe et al. (2014) proposed that the retained DBBM was resistant to resorption and slowed healing at the site. This delayed healing pattern was also demonstrated by Geurs et al. (2014).

Chan et al. (2013) concluded that the connective tissue content was decreased when using xenografts in both GBR and SS techniques, with this tissue volume replaced by the retained 15% to 36% of graft particles. The results from this study, indicated that the residual graft in the GBR and SS ARP techniques resulted in less bone formation, whilst maintaining similar levels of connective tissue matrix to that of unassisted healing.

Although the graft matrix was well tolerated, with no foreign body reaction observed during imaging, the presence of the DBBM was seen to promote a slower bone healing and remodelling rate than the control (Nevins et al., 2006, De Coster et al., 2011, Serino et al., 2008). The reduced remodelling rate

potentially affecting the quantity and the quality of the regenerated bone (Froum et al., 2002; Mardas et al., 2010; Horvath et al., 2013; Hsun-Liang et al., 2013), and the retained graft matrix reducing the volume of connective tissue (Lindhe et al., 2014, Dies et al., 1996, Araujo et al., 2008).

10.4.2 Unassisted socket healing

Unassisted healing was associated with a reduced volume of new bone formation in the coronal area, a failure to re-establishment the lamella bone cap over the socket opening and increased connective tissue formation. Human studies (Carmagnola et al., 2003, Araújo et al., 2012, Araujo and Lindhe, 2005), indicate that when critical size defects were present (Donos et al., 2004), physiological healing does not occur spontaneously or predictably, with incomplete closure of the defect site reported. This observation was seen in the Control group, where incomplete coronal bone reconstruction and regeneration occurred. Chan et al. (2013) observed that the mean percentage of vital bone and connective tissue in natural healing sockets was 38.5% (± 13.4%) and 58.3% (± 10.6%). Nevertheless, the percentage bone volume and area in this PhD consistently demonstrated a higher level of new bone formation at Control sites in comparison to GBR and SS.

10.4.3 ARP with membrane placement

The structural integrity of a GBR barrier material and its peripheral adaptation to the boundary bone is considered essential, as it prevents cellular invasion and promotes new bone formation (Kostopoulos and Karring, 1994, Donos et al., 2002a, Donos et al., 2002b, Donos et al., 2002c, Donos et al., 2002d, Retzepi and Donos, 2010). SS ARP techniques advocate primary tissue closure using a collagen matrix or gingival graft, which functioned as a "protective seal", preventing the loss of the underlying graft matrix and the ingress of bacteria and chemical irritants into the augmented site (Landsberg and Bichacho, 1994, Cook and Mealey, 2013, Barone et al., 2008, Perelman-Karmon et al., 2012, Lindhe et al., 2014). In this study, the tissue occlusion effects from GBR, were observed to be more effective than the SS matrix, as the collagen matrix was observed to have a greater incidence of breakdown or dehiscence. When disruption or loss of the membrane or matrix barrier function was noted in either of the GBR and SS groups, it resulted in increased sequestration of the graft matrix, a lower percentage of new bone formation and graft osseointegration, with greater fibrous encapsulation of the residual graft matrix (Elgali et al., 2014, Simion et al., 1994).

The breakdown of a covered Bio-Guide membrane (Tal et al., 2008, Moses et al., 2008, Calciolari et al., 2018b), or Mucograft® matrix (Ghanaati et al., 2011) is reported to occur over a 30 day healing period. Tissue degradation was noted to be more advanced in this study and was attributed to the membrane's exposure to the oral environment and the action of proteolytic enzymes (Rocchietta et al., 2012). The early membrane degradation influences the mechanism of GBR and SS bone healing,

contributing to unfavourable grafting outcomes (Garcia et al., 2018). Faster resorption of the collagen barrier or matrix leads to increased fibrous tissue formation (Donos et al., 2004), with disruption to the occluding layer (Donos et al., 2002b, Donos et al., 2002d, Donos et al., 2002a, Donos et al., 2002c) also leading to lower levels of new bone formation within the socket (Mardas et al., 2010). The improved longevity and stability of the GBR barrier membrane was credited for the statistical difference in new bone formation when comparing GBR and SS ARP techniques.

When new bone formation was observed in the bone samples, it was principally located in the apical and mid sections of the bone core and the peripheral area of the coronal section. Evidence of coronal bone formation was only seen with the GBR technique, when the membrane remained intact. Donos et al. (2004) indicated that fibrous encapsulation of graft particles can occur, even when the GBR barrier membrane is correctly applied. He reported that new bone formation and graft integration was commonly seen at the periphery of a bone defect, with the central healing area undergoing fibrous encapsulation of the graft. An increased rate of membrane resorption, and local breakdown of the central occlusive and barrier function, was attributed to the bone healing disparity. New bone formation was eventually observed under this central fibrous area (Donos et al., 2002a, Donos et al., 2002b, Donos et al., 2002c, Donos et al., 2002d), buthealing was observed over an extended period. Carmagnola et al. (2003) confirmed similar findings in the extraction socket, reporting that the central region was composed of mainly connective tissue and encapsulated graft matrix.

Turri et al. (2016) indicated that a stable GBR membrane appeared to create a bio-active compartment, which had a direct effect on healing. Examination of protein expression at GBR sites in the animal model, indicated that proteins and cellular activity were highest at day 7, involving pathways associated with cell proliferation, osteoblast precursor differentiation and bone development (Calciolari et al., 2018a). Animal microarray gene expression also demonstrated the importance of stabilisation of the GBR site at day 7 and 14, as gene markers changed from an initial inflammatory phase to progressive maturation of the granulation tissue into woven bone (Donos et al., 2011, Al-Kattan et al., 2017). If the GBR or SS membrane/matrix integrity is broken down during this key period, it would potentially affect the ability to produce the regulatory proteins leading to regeneration of the bone matrix (Calciolari et al., 2018b). The use of a membrane or matrix, with a greater structural integrity (Buser et al., 1999) during a healing period of up to 6 months, may have advantages for GBR or SS ARP techniques (Calciolari et al., 2017).

Qualitative analysis indicated that variable levels of osseointegration was present in the three test groups, presenting as bone bridges between the graft particles in the apical and mid sections of the biopsy. Occasionally, void spaces were seen in the mid socket region, due to incomplete placement of the graft matrix. These sites were regularly seen to have a higher level of new bone formation. Whilst a graft matrix has been recommended to improve membrane stability and provide a support scaffold,

GBR alone may be associated with improved bone osteogenesis (Donos et al., 2005, Hämmerle et al., 1997), and greater new bone formation.

10.4.4 Innovation

Qualitative assessment of tissue changes is routinely undertaken when examining bone samples, as the human eye is exceptional at pattern recognition and can detect small changes in the bone architecture. In cases where detection of subtle quantitative changes is critical, more sensitive methods are required. Two-dimensional stereology can provide additional information and is useful in many cases. However, the analysed image may not be reflective of the entire tissue sample and can risk assessment bias. A high resolution MuCat XMT scanner allows non-destructive visualisation of the bone core through multiple image slices, with the high-definition tomography allowing for easier interpretation of the compositional structure of the bone and the involvement of the complete data volume. This methodology is distinctive in the literature, with XMT imaging in combination with the developed software, ensuring that an independent quantitative analysis of the healed tissue was undertaken. The ability to vary the bone grey scale in the analysis does introduce a risk of bias, but it ensures that local difference in image contrast can be accounted for. Comparison of the BSE-SEM and XTM images, demonstrated differences in bone and graft composition and facilitated the measurement of the level of the osseointegration in the core biopsy. This measurement would have been impossible to calculate from the BSE-SEM images alone. Future ARP studies should consider utilising this methodology with an increased sample size, to determine the histomorphometric difference in the bone healing.

The ability to differentiate bone healing at three different levels in the sore sample and to produce a level of osseointegration between the bone and graft particles was seen as being unique and allowed for a greater understanding the healing characteristics in the three test groups. One limitation was that the osseointegration percentage was higher, when only a small area of new formation was present. The amount of new bone formation and osseointegration should be reviewed together, during comparative analysis.

10.5 Conclusion

GBR was found to produced similar levels of bone formation to the SS technique but was associated with more osseointegration between the xenograft DBBM matrix and new bone. The new bone formation was mainly confined to the middle and apical areas of the socket, in both the GBR and SS techniques. Fibrous encapsulation of the graft was seen coronally in both GBR and SS test groups. Exposure of the collagen barrier and matrix to the oral environment influenced the integrity of the healing site, affecting the cellular and inflammatory pathways. This change may influence the bone healing response. Loss of membrane integrity was observed in both GBR and SS techniques, but was

more common with SS. When loss integrity of the membrane was observed, it was associated with a reduction in new bone formation. The control group was found to create the most new bone formation, with the DBBM graft observed to negatively affecting new bone formation. Connective tissue percentage remained the same in both ARP and Control groups.

Whilst XMT volume assessment of the trephined bone samples did not show a statistical difference to that of the BSE-SEM measurement, the multiple slice analysis proved more effective at calculating the histomorphometric composition of the bone sample, potentially reducing the risk of selection bias from individual BSE-SEM images. No visual evidence of cellular resorption of the graft matrix was observed, following iodine imbibition and BSE-SEM investigation of the bone core.

Chapter 11

Implant Survival and Success Criteria and Need for Bone Augmentation Following ARP

Material, Methods, Results and Discussion

11.1 Introduction

Successful implant rehabilitation is based on effective osseointegration of the implant and the establishment of a stable peri-implant soft tissue collar (Saravi et al., 2020, Avila-Ortiz et al., 2020a). As tissue remodelling and contour change is an inevitable consequence of exodontia (*Fig. 49*), the maintenance of the existing bone and soft tissue is a prerequisite for implant survival and success (Horváth et al., 2013), the achievement of an aesthetic prosthetic restoration (Cosyn et al., 2021, De Lange, 1994), and a simplification of the surgical implant treatment protocol (Jonker et al., 2021, Vanhoutte et al., 2014, Fischer et al., 2018).

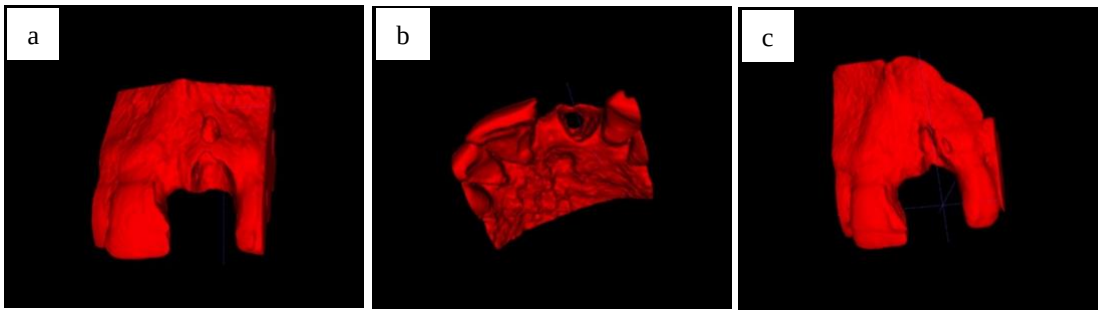


Figure 49. *Three CBCT volume rendering reconstructions demonstrating vertical and horizontal tissue loss following tooth extraction. a) and b) Socket shape immediately after the extraction. c) alveolar bone contour at 4 months healing.*

The aesthetic outcome of implants placed in the anterior maxilla is particularly challenging, as the height of the lip line and the extent of the gingival display, can affect the visibility and profile of the prosthetic restoration (Jonker et al., 2021). The achievement of both a functional and aesthetic successful outcome, is dependent on placement of the implant in the correct 3D spatial alignment (Kois, 2004, Lang and Zitzmann, 2012), the establishment of a stable and cleansable emergence profile (De Lange, 1994) and an idealised shape for the implant supported restoration (Belser et al., 2004).

ARP techniques are associated with preservation of the bone and soft tissue socket contour, resulting in a healed alveolar ridge shape able to support implant success. The graft matrix acting to promote physiological healing, and a histological bone composition compatible with successful osseointegration and long-term implant success. However, GBR and SS ARP surgical protocols, are associated with bone and soft tissue grafting procedures, which can alter the percentage of new bone formed in the healed socket and leave an unresorbed residual graft matrix (Alkan et al., 2013, Carmagnola et al., 2003). This residual graft matrix may potentially disrupt the bone and soft tissue healing, impacting on the subsequent implant osseointegration process, and survival and success rates post loading. Studies

have evaluated implant success by examining parameters such as immobility, peri-implant radiolucency, the presence of infection in the peri-implant soft tissues and long-term prosthetic stability (Albrektsson et al., 1986, Smith and Zarb, 1989, Buser et al., 1990, Misch et al., 2008, Albrektsson and Zarb, 1998).

This PhD chapter compared the effects of GBR and SS ARP techniques, on implant success and survival characteristics. Additional outcome factors assessed, included the ability to use a prosthetically determined implant placement protocol and the need for additional ridge augmentation, prior to implant placement. Unassisted healing acted as the Control, with implant placement planned at 4 months healing.

11.2 Materials and methodology

Study Population

The study population, inclusion and exclusion criteria are outlined in the description provided in Chapter 4, section 3. The ARP and Control surgical extraction protocol is also described in Chapter 4, section 5. In summary, forty-two patients were split into 3 test groups (n=14 per group) as following: Group 1(test): GBR using a combination of deproteinized bovine bone mineral (DBBM) and a porcine collagen membrane/barrier; Group 2 (test). A SS technique combining the use of DBBM and a porcine collagen matrix; Group 3 (Control). Unassisted socket healing.

11.2.1 Surgical Protocol

In the ARP test and Control groups, a CBCT radiograph was taken at 4 months post tooth extraction. The CBCT image was recorded with the patient wearing a custom-made radiographic stent, with the stent designed to outline the position of an idealised prosthetic replacement for the missing dentition. The surgical treatment protocol for the patient was planned according to the alveolar bone width calculated on the CBCT image and the radiographic outline of the prosthetic tooth. The long axis of the implant was aligned to facilitate a screw retained implant supported restoration. Implementation of the surgical plan was achieved through the construction of a clear surgical stent, which acted to guide both the drilling sequence and the implant fixture placement, during the surgical procedure. The stent was designed to cover three teeth either side of the surgical area, for stability.

At the surgical implant placement appointment, a horizontal incision was undertaken on the crest of the alveolar ridge, extending the full length of the edentulous space. Two vertical relieving incisions were then placed on the mesial aspect of the adjacent teeth, extending vertically into the free gingival margin. These incisions allowed a full thickness mucoperiosteal flap to be raised, to expose the buccal and palatal aspect of the alveolar process and allow access to the healed extraction site. The surgical stent

was then placed on the dentition, prior to preparation of the site using a surgical trephine (STOMA, Germany) with an external diameter of 3mm. The custom stent being used to align the drill angulation according to the pre-planned design orientation. Further preparation of the site was then undertaken according to the Nobel implant surgical protocol, using the drill sequential outlined in the NobelBiocare (2014) implant fixture preparation guidelines. The ability to exactly follow this idealised protocol was noted, with any violations documented. It was anticipated that implant placement variation may result from labial implant placement following excessive buccal alveolar bone resorption, or to ensure maximum bone encasement, to promote primary stability of the fixture (Kois, 2004). The idealised prosthetic position was achieved when the buccal aspect of the implant platform was at least 1 mm or more palatal to the future buccal aspect of the prosthetic restoration (Buser et al., 2004), with the implant stability assessed by an insertion torque of more than 30N and the surgeons' perception of primary implant stability (O'Sullivan et al., 2004).

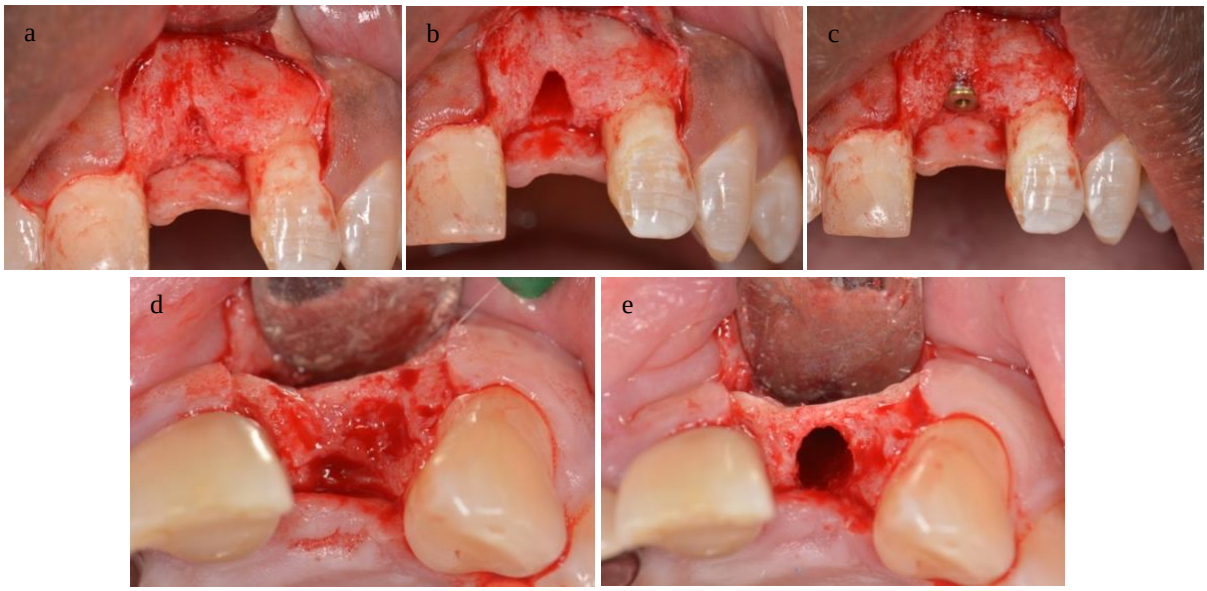


Figure 50. *Picture of the Alveolar bone crest demonstrating per-operative ridge contour and post-operative osteotomy site preparation, prior to Nobel Parallel RP implant placement. a) Healed alveolar ridge after SS ARP at 4 months. (b) prepared osteotomy site 21 position. (c) Implant placement with buccal dehiscence. (d) Healed alveolar ridge after GBR ARP at 4 months healing. (e) Prepared osteotomy site with a thick buccal contour of above 2mm.*

11.2.2 Buccal bone augmentation at implant placement

Following surgical preparation of the implant osteotomy site, the buccal alveolar bone wall was scrutinised for localised bone dehiscence or fenestration defects. The investigator recorded the

requirement to undertake additional GBR bone augmentation at the time of implant placement, to facilitate bone regeneration around exposed implant threads or to correct anatomical defects (*Fig. 51 and 52*). Augmentation was performed using a DBBM material and a resorbable collagen barrier (Bios-Oss® and BioGide®, Geistlich, Wolhusen, Switzerland). Aesthetic GBR contour augmentation was undertaken, when less that 2mm of buccal bone remained, or when the residual buccal bone profile had a horizontal discrepancy or marked asymmetry when compared to the contralateral tooth. Augmentation of this defect area, improving future bone stability and improving the aesthetic contours of the site, facilitating implant reconstruction (Buser et al., 1996, Jonker et al., 2021, Thoma et al., 2020a).

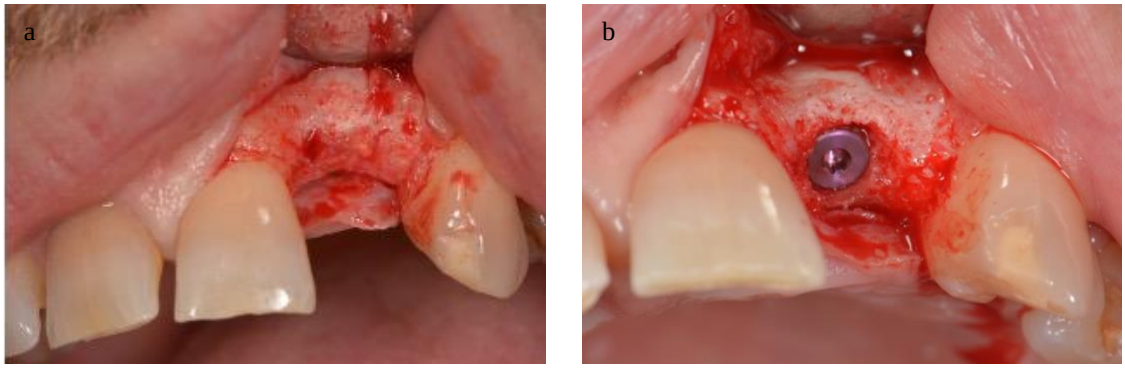


Figure 51. *Alveolar bone crest before and after osteotomy preparation, where no bone augmentation was required at implant placement. (a) healed alveolar ridge after GBR ARP at 4 months, (b) Nobel implant fixture in position, with no requirement for buccal bone grafting.*

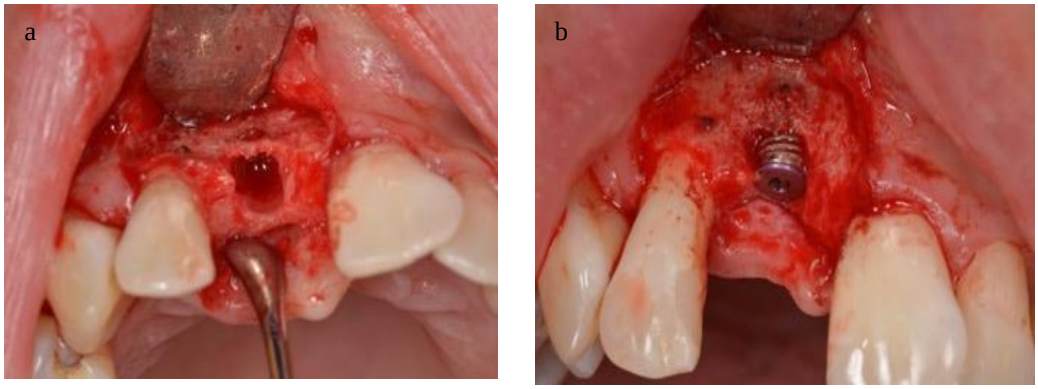


Figure *52.* *Pictures of surgical osteotomy site, where additional GBR was required at implant placement to cover exposed implant threads (dehiscence). (a) Alveolar osteotomy site demonstrating unassisted healing, demonstrating both bone dehiscence and fenestration, (b) Nobel Parallel implant in situ demonstrating requirement for additional bone grafting*

11.2.3 Prosthetic reconstruction of the implant fixtures

All edentulous sites were situated in the anterior maxilla and were restored using a Nobel Biocare bone level implant. Eight NobelSpeedy, twenty-eight NobelParallel and six NobelActive implants were used in the study (Nobel Biocare AB, Gothenborg, Sweden). Implant supported restorations were constructed using seven cement retained (5 Nobel Speedy and 2 Nobel Parallel) and thirty-five screw retained restorations. The cement retained restorations comprised a custom zirconia abutment and an e.max / feldspathic layered crown (IPS e.max Ivoclar Vivadent, Ellwangen, Germany). The screw retained crown's prosthetic structure included a zirconia abutment, angulated screw channel, Omni screw and a feldspathic/zirconia layered crown (Nobel Biocare AB, Gothenborg, Sweden).

Supragingival debridement and oral hygiene instructions was provided for the patient at the review visits between implant fixture placement and placement of the implant supported crown. The patient was then discharged to their General Dental Practitioner for regular maintenance over the 6-to-12-month assessment period.

11.2.4 Implant survival and success criteria

Implant survival and success was recorded at 6 and 12 months post implant loading. Implant survival indicated whether the implant was still functionally present in the mouth, whilst implant success evaluated the implant according to the criteria proposed by Albrektsson et al. (1986), Buser et al. (1990), and Ong et al. (2008). The assessment of proximal or coronal bone loss was undertaken using a periapical radiograph. Standardisation of the radiograph assessment position was achieved using a customised putty matrix placed on an X-ray Rinn sensor holder (RINN XCP-2001 kit Dentsply Serona). This matrix ensured reproducibility of the assessment at the 6 and 12 month review appointment. Radiographic bone loss was measured using the linear measurement tool on the VixWin (Kavo Dental 2020) viewing software.

The evaluation of implant success and survival was undertaken using two different classification systems. The work by Albrektsson et al. (1986), Esposito et al. (1998), Buser et al. (1990) summarised implant success and survival as follows:

A successful dental implant

- Absence of any continuous peri-implant radiolucency based on radiographic findings.
- Absence of implant mobility.
- Absence of a recurrent peri-implant infection with suppuration (where an infection is termed recurrent if it is observed at two or more follow-up visits after treatment with systemic antibiotics).

- Bone level changes evaluated on periapical radiographs around dental implants less than 1 mm during the first year after placement.

A failing but treatable dental implant

- A mobile dental implant was considered a failing implant, but not a lost dental implant, as it still could osseointegrate.

Failed dental implant (lost)

- Dental implant loss

Ong et al. (2008) advised that a successful dental implant was considered a dental implant fulfilling the following criteria:

1. Absence of mobility (Buser et al.1990).
2. Absence of persistent subjective complaints (pain, foreign-body sensation and/or dysaesthesia) (Buser et al. 1990).
3. Absence of recurrent peri-implant infection with suppuration (Buser et al. 1990).
4. Absence of a continuous radiolucency around the implant (Buser et al. 1990).
5. No pocket probing depth (PPD)> 5mm (Mombelli & Lang 1994, Bragger et al. 2001).
6. No PPD > or =5mm and bleeding on probing (BOP) (Mombelli & Lang1994).
7. After the first year of service, the annual vertical bone loss should not exceed 0.2mm (mesially or distally) (Albrektsson et al. 1986 and Albrektsson & Isidor 1994).

If a dental implant was considered a failure, the dental fixture was removed. Following removal and treatment of the site, a new dental implant would be placed, but this implant fixture was not entered in this study. Any dental implant that was showing excessive bone loss, such as radiolucency or infection, would be treated in the manner best suited to the well-being of the patient, including treatment to save the dental implant. Treatment may include surgical intervention to resolve infection and or sequestra and may comprise administration of topical or systemic antibiotics. Such events and treatments would be recorded on the Adverse Event form.

Photographs of the completed restorations were taken with a digital camera (Nikon D80 and Nikon SB R1C1 speedlight commander kit; Nikon Corporation Tokyo, Japan) immediately following implant loading and at the 6- and 12-month review.

11.3 Statistical analysis

The study was originally powered to assess radiographic bone changes following 4-month healing. The data is therefore presented in a descriptive format, for the qualitative outcome measures. All data was entered in a computer database, proofed for entry errors and loaded in the SPSS statistical software package (v.22). Numerical data in the ARP test and control groups was presented as the mean ± standard deviation (SD), with the frequency distribution within each group indicated with numbers and proportions. The chi-square test and two-sample t-test was used to compare intergroup differences in distribution proportions and means, respectively.

11.4 Results

All patients underwent extraction of a single rooted tooth in the upper anterior maxilla (15- 25 position), with thirty-six central incisor teeth, one canine and five premolar teeth removed. Two premolars were randomly allocated to the GBR group, with a canine and premolar tooth included in the SS test group and two premolars allocated to the Control.

11.4.1 Implant placement feasibility and additional bone grafting at implant placement

All patients in the GBR, SS, and Control groups (100%), were able to realise implant placement according to a prosthetically driven protocol, whilst still achieving adequate primary stability. In the GBR group, 57% (8 patients) required bone augmentation at implant placement, with 28.5% (4-patients) of these cases undergoing augmentation due to bone dehiscence, or aesthetic contour augmentation. In the SS group, 64% (9-patients) required augmentation at implant placement. 50% (7-patients) of these cases were due to implant dehiscence, with 14% (2-patients) undertaken to facilitate contour augmentation. No cases of implant fenestration were documented in the GBR or SS groups.

The Control group required bone augmentation at the time of implant placement in 85% (12-patients), with 71% (10-patients) due to the presence of bone dehiscence and 14% (2-patients) due to a fenestration defect. No bone augmentation was undertaken in the Control group for contour augmentation alone. The Chi-square statistic was used to examine the difference in effect size. A significant difference was found when comparing the GBR and Control groups for augmentation due to implant dehiscence and fenestration ($p=0.03$).

11.4.2 Implant success and survival

Implant survival was 100% in the GBR and SS test groups and the Control, with no implant osseointegration failures recorded at the 12 month review. Implant success, based on the Albrektsson et al. (1986) and Buser et al. (1990) criteria, was 100% in the GBR group, while two patients in the SS (14%) and one patient in the Control groups (7%) failed to fulfil the criteria at 6 months and 12 months. This failure was due to radiographic proximal bone loss great than 1mm (1.55 and 1.2 mm SS / 1.2mm Control) after implant loading. Two of the SS patients were restored using a Nobel Active implant, with the Control group implant restored using a NobelSpeedy fixture.

The success criteria outlined by Ong et al. (2008) was fulfilled in all the GBR patients at 6 months, whilst one patient in the SS group and one patient in the Control, were classified as a failing but treatable implant, due to radiographic bone loss of 1.5 mm and BOP at the implant site.

At 12 months, implant success (Ong et al., 2008) was still 100% in the GBR group, but had reduced to 86% in the SS group and 86% in the Control. The reasons for not fulfilling the success criteria in the SS and Control group was either a PPD > 5 mm with or without the association of BOP, or a radiographic bone loss >1.5 mm on one aspect of the implant. FMPS and FMBS scores were recorded at less than 10%, for all patients during treatment. Pictures of the successfully loaded implants at 12-months are presented in *Fig. 53, 54* and *55*.

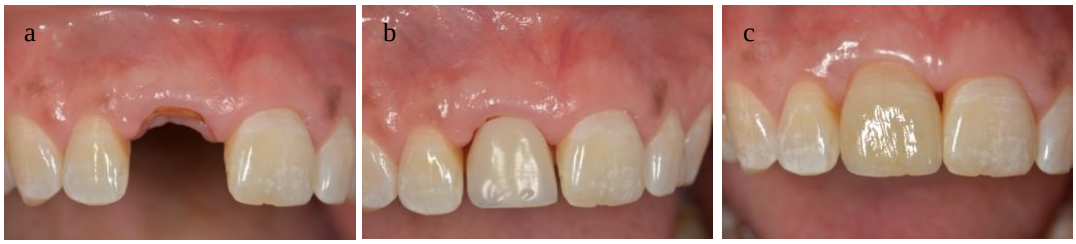


Figure 53. *Pictures demonstrating fracture of the 11 incisor and completed implant supported restoration at 12 months. (a) Fractured 11 incisor prior to extraction. (b) Temp acrylic denture after root extraction and SS ARP. (c) Prosthetic crown at 12 month healing, recording tissue loss on the mid-buccal and distal papilla area.*

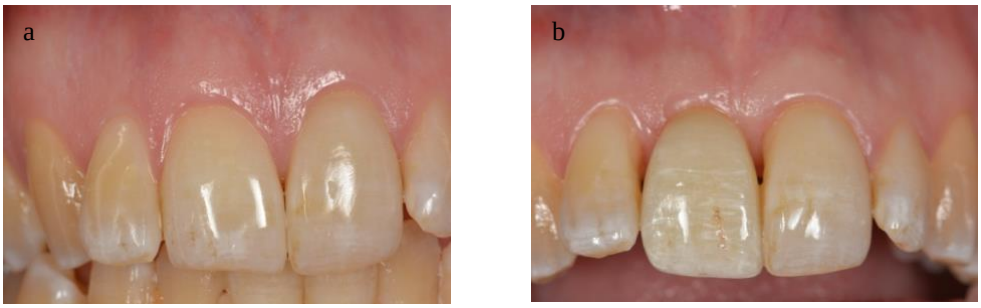


Figure 54. *Pictures demonstrating 11 with external cervical resorption and completed implant restoration. (a) 11 incisor presenting with external root resorption. (b) 11 prosthetic implant crown at 6 months healing, with a slight loss of the mesial and distal papilla and a change to the peri-implant soft tissue texture.*

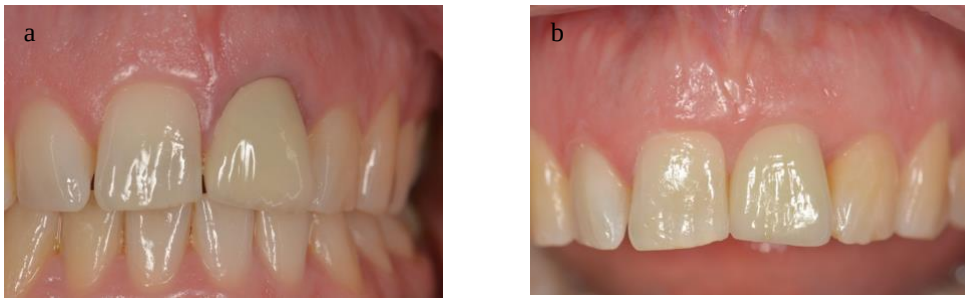


Figure 55*. Picture demonstrating endodontically compromised 21 incisor and successful implant supported restoration at 12 months healing. (a) 21 incisors presenting with endodontic complication. (b) 21 prosthetic implant crown demonstrating minimal loss of the papilla in the mesial area and only slight loss distally.*

11.5 Discussion

Recent studies have sought to explore whether contour preservation from ARP, translates into a reduced need for additional bone augmentation at dental implant placement, and whether the healed bone composition of the extraction site, was compatible with implant osseointegration and success (Avila-Ortiz et al., 2019, Barone et al., 2013b). There is also a general lack of homogeneity within the dental literature, when reporting on the survival and success rates for dental implants. This is due to the adoption of differing assessment criteria, which have variation in the level of biological bone changes accepted over a specific assessment period (Simonis et al., 2010). Many studies solely reporting on survival as an outcome, with no mention of success (Lang et al., 2012).

11.5.1 Implant survival

The results of this study indicated that ARP using a DBBA and collagen membrane (GBR) or matrix (SS) surgical technique, was compatible with implant survival, with 100% of implants still in situ at 12 months post loading. The study by Barone et al. (2012) found a similar, but slightly lower level of implant survival (95%) when using a DBBM graft, with the survival levels being similar in both the test and unassisted healing group. The implants were however placed after 7 months bone healing, with the review undertake at 3 years. Sandor et al. (2003) found a 100% survival rate for implants placed in an ARP site after placement of a coral graft, with results assessed over a 3 to 7 year period, with van Kesteren et al. (2010) indicating a 100% survival rate for a FDBA ARP graft, when appraised over a 6 month healing period. Survival rates for implant were also assessed in ARP studies using a DBBM and Straumann bone ceramic graft, with Patel et al. (2013) indicated an 84.6% survival rate with a bone ceramic group and 83.3% with Bio-Oss®, when review 8 months after implant loading. Aghaloo and Moy (2007) indicated a similarly higher level of implant survival rate (95.5%), when using a GBR and DBBM and ARP technique, with the retrospective analysis undertaken by Apostolopoulos and Darby (2017), indicating a 100% survival rate for implants placed in augmented DBBM sites in the anterior maxillary implants after 24 months loading.

The systematic review by Moraschini et al. (2015), examined the cumulative survival rates for implants from 27 trials over a 10 year period, indicating a mean survival rate of 94.6%, with an associated marginal bone loss of 1.3 mm. These results suggest that implant placement in an ARP site, predictability leads to successful osseointegration of the fixture, and a survival rate which is comparable to ungrafted sites.

11.5.2 Implant Success

The assessment of implant success was seen to vary in this study, dependant on the timeline of the examination and the criteria used for the assessment. Outcomes were dependant on whether the Albrektsson et al. (1986) or Ong et al. (2008) evaluation criteria were used, with the observed differences resulting from bone level changes during the first years, timeline for assessment and attachment loss as a consequence of peri-implantitis.

Lang et al. (2012) indicated that most marginal bone loss took place in the first year after implant placement, with Canellas et al. (2020), proposing that survival and success criteria should be assessed after 7 months, to ensure that biological complications were observed and accounted for. Kassim et al. (2014) suggested that the adoption of ARP techniques may require a commitment to both a delayed assessment and restorative protocol, as the presence of a residual graft may delayed bone healing. Difficulty in achieving high insertion torque in sockets grafted with Bio-Oss® at 4 months post-extraction has also been reported by Felice et al. (2011), supporting the requirement for an extended

healing period (Kassim et al., 2014). This potential delay in bone healing may impact on the timeline for implant placement, affecting the costing and prosthetic requirements for the planned restorative treatment (Kassim et al., 2014).

The results in this study indicated no difference in implant success in the ARP and Control group, at 12 months loading (84%), conforming to the success findings reported by Crespi et al. (2020), who found a success rate of 88.1% in both a porcine GBR ARP group and unassisted healing at a 10 year review. Busenlechner et al. (2016) observed 98.4 % implant success with a SS and DBBM technique and a 97.9% GBR DBBM combination after 3 years.

The systematic review undertaken by Tonetti et al. (2019), indicated that ARP grafted sites demonstrated no difference in implant success when compared with unassisted healing, after a minimal of 12 months function. The review undertaken by Zhou et al. (2019) indicated an implant success rate of 98.6% in ARP augmented sites, when examined over a 6 month to 10-year period. Zhou et al. (2019) noted that less tissue complications were observed in highly aesthetic implant case, when ARP had been undertaken at an extraction socket with an intact buccal socket contour. This treatment scenario resulted in an improved implant success rates of 98.6% following ARP, Vs. 89.6% following immediate implant placement.

Other published systematic reviews (Avila-Ortiz et al., 2014a, Chan et al., 2013, Vignoletti et al., 2012) have concluded that whilst ARP may improve bone dimensions compared with extraction alone, the long-term effects of ARP on implant success and peri-implant tissues remain unclear.

11.5.3 Implant bone augmentation

Whilst GBR, SS and Control groups facilitate implant placement according to a prosthetically driven protocol, the requirement for additional bone augmentation was reduced in the GBR and SS groups. Whilst no statistical difference was observed between groups, the reduction in patient's numbers (3/4) requiring additional augmentation would be clinically significant. The lower number of GBR patients, who required bone augmentation due to a fenestration defect at implant placement, supports the assumption that GBR is more effective at protecting the augmented buccal socket wall dimension.

Horváth et al. (2013) described that only limited evidence supported the clinical benefit of ARP, namely, a reduced need for further augmentation in conjunction with dental implant placement. Tonetti et al. (2019) discuss this requirement in the XV European Workshop Periodontology, indicating that the need for additional grafting at implant placement was lower with ARP, but additional grafting of the augment socket may still be necessary. The systematic review by Atieh et al. (2021) found no evidence of a significant difference for the need for additional augmentation when examining 4 studies.

However, the evidence is contradictory, as Weng et al. (2011) indicated that unassisted healing sites, had a five times increased risk of requiring alveolar ridge augmentation at dental implant placement, with the meta-analysis by Willenbacher et al. (2016) determining that whilst dental implants could be inserted into a prosthodontic-driven position without further augmentation in 90.1% of ARP patterns, this scenario was only present in 79.2% of unassisted healing socket.

It was concluded that implants placed into grafted extraction sockets exhibited a clinical performance similar to implants placed into non-grafted sites, in terms of implant survival and marginal bone loss. However, grafted sites allowed placement of larger implants and required less augmentation procedures at implant placement when compared to naturally healed sites, which may reduce the interventional requirement for patients and reduce the complexity of subsequent treatment. This reduced surgical complexity impacting on the overall cost for implant treatment.

11.5.4 Study limitations

A limitation of this study is the phenotypic characteristics of the enrolled patients, as the extent of bone modelling after extraction, has been found to be depends on the facial bone wall thickness. Whereas thin bone phenotypes (buccal socket < 1 mm) often show progressive bone resorption and extensive vertical and horizontal buccal bone loss, thick bone phenotypes (buccal socket > 1 mm) show only limited resorption (Araujo et al., 2006, Chappuis et al., 2017, Avila-Ortiz et al., 2020a, Araújo et al., 2015, Araujo and Lindhe, 2005, Tomasi et al., 2010). All patients in this study were required to have a thick periodontal phenotype and by association a thick bone phenotype. This inclusion criteria may have reduced the bone resorption characteristics seen in both the ARP and Control groups, reducing the augmentation requirement at implant placement and influencing the ability to adopt a prosthetically determined surgical protocol.

The inclusion of both central incisor, canine and premolars in this investigative study, may have also introduced an element of selection bias, as different socket resorption patterns may be experienced by specific teeth, due to variations in alveolar bone configuration. If a larger sample population is investigated in future ARP studies, a liner statistical analysis approach may be favoured, as it would allow for the known variations in the alveolar bone dimensions to be accounted for.

11.5.5 Future research direction

Further research is now required, using a higher-powered study, to evaluate implant success following ARP. The adoption of a universally adopted assessment criteria for implant success is a necessity, as it would allow for the comparison of outcomes from different ARP studies. The implant success criteria proposed by Ong et al. (2008), would appear to offer researchers an advantage in accomplishing this aim, due to the comprehensive nature of the assessment.

11.6 Conclusion

Implant success and survival rates were not affected by ARP, with no difference in outcome noted when comparing the GBR and SS ARP test groups and the control. The ability to place an implant according to a prosthetic surgical protocol, was not superior with ARP, but GBR appeared to offer an advantage over SS ARP and the Control, when augmentation requirements were considered.

Chapter 12

General Discussion, Concluding Remarks and Future Research Direction

12.1 Study structure

This PhD thesis was designed to provide advice on ARP techniques for military dentists, to aid in their treatment planning of trauma patients. It was anticipated that the research outcomes would influence the immediate management protocols for traumatised patients, whilst facilitating force preparation of the military cohort. An enhanced understanding of the risks and benefits of ARP, would ensure that patient rehabilitative options, focused on the attainment of an implant based prosthetic solution.

The study design took inspiration from the 4th European Association of Osseointegration (EAO) consensus conference (Sanz et al., 2015) and the research findings from several systematic reviews (Vignoletti et al., 2012, Horváth et al., 2013, Avila-Ortiz et al., 2014a, Vittorini Orgeas et al., 2013, Postlethwaite et al., 1978, Cardaropoli et al., 2014, Jung et al., 2013b). These reviews indicated that there was insufficient robust evidence to recommend a specific ARP technique or biomaterials. Additional longitudinal studies were required to strengthen the evidence base and elucidate on the impact of ARP on implant success, bone and soft tissue dimensional changes, new bone formation and patient-based outcomes. Whilst further research has now been published and additional evidence provided (Jonker et al., 2021, Sapata et al., 2020), the recent Systematic Reviews by Atieh et al. (2021) and Couso-Queiruga et al. (2021) concluded that a lack of consensus was still present, when considering the impact of ARP on tissue dimensional change, implant survival and implant aesthetic outcomes. The clinical differences associated with different ARP barrier materials techniques was also unclear. The requirement for better quality longitudinal studies remains, with a need for more evidence from high quality RCT's to guide clinicians.

This PhD project was designed to specifically investigate two distinctive ARP techniques and examine the difference in bone and soft tissue healing characteristics. It was hoped that the innovative nature of the research, the new ideas adopted, and the evolved methodology, would assist in understanding ARP's influence on socket healing.

The PhD thesis included five investigative areas, namely: a systematic review of implant-based outcomes following ARP, a systematic review of hard and soft tissue changes following alveolar ridge preservation and an RCT which investigated; (a) radiographic bone changes and patient outcome measures, (b) soft tissue contour change, (c) the histological bone composition after socket healing and (d) implant success / survival, and the need for additional bone grafting at implant placement.

12.2 Does ridge preservation following tooth extraction improve implant treatment outcomes?

The scientific development of dental implant systems, in combination with a comprehensive understanding of the osseointegration process, has made implant treatment in the maxilla highly predictable. Improvements in the predictability of implant survival and success, has also made their use in the replacement of missing teeth, the preferred option for many patients. ARP techniques have evolved as a clinically relevant protocol, under the assumption that their adoption encourages tissue healing, limits the requirement for future ridge augmentation and simplifies future surgical processes (Horváth et al., 2012, Vignolleti et al., 2012, Wang and Lang 2012, De Risi et al., 2013). The first study in this PhD, Chapter 2, examined their impact on implant placement feasibility, need for additional bone augmentation, proximal bone loss and patient-based outcomes.

Impact of ARP on Implant placement

The Systematic Review was structured in an original format, splitting the analysis into two separate sections. Focused Question 1 asked if there was an additional benefit of alveolar ridge preservation techniques, over unassisted healing, when considering implant placement feasibility and implant success criteria? Focused question 2 asked; what was the average incidence of implant placement feasibility, need for further augmentation, implant survival / success and marginal bone loss, following different alveolar ridge preservation techniques? The use of both controlled and case series, ensured that as much research data was included in the review. This methodology allowed often neglected sources of information, to be included in the summative results. Direct data capture from authors, enabled the addition of unpublished data into the review, ensuring a comprehensive assessment of all the available research information.

The findings indicated that there was no clear evidence that a specific ARP procedure or graft matrix, increased implant placement feasibility, when compared to unassisted healing. The review summarised that whilst dental implants could be placed in most cases, the requirement for additional bone augmentation at implant placement varied significantly. The need for further augmentation ranged between 0 - 15% in the ARP treated sites and 0 - 100% in unassisted socket healing sites. The requirement for bone augmentation was statistically less when ARP was performed (Relative risk: 0.15, 95% CI: 0.07 to 0.3). However, limited data was available to assess the need for augmentation when using a SS technique. These results are in accordance with earlier research studies, who indicated a 0%-40% reduction in the augmentation requirement with ARP, and up to a 100% requirement for unassisted healing (Avila-Ortiz et al., 2019; Lim et al., 2020; Mardas et al., 2015; Thoma et al., 2020).

Implant Success

The review observed that all implants in the SS, GBR and socket grafting groups survived and experienced high success rates. The success rates ranged between 95.2% to 100% for ARP sites and 90% to 100% for the Control. The success criteria used by examiners included immobility, peri-implant radiolucency and infection of the peri-implant soft tissues (Albrektsson et al., 1986; Smith and Zarb, 1989; Buser et al., 1990; Albrektsson and Zarb, 1998; Misch et al., 2008; Annibali et al., 2009). Whilst these criteria are extensive, they failed to consider other qualitative outcome measures, including patient satisfaction, soft tissue profilometry and implant aesthetic outcomes (Buser et al., 2004, Cardaropoli et al., 2006). The review suggested that future studies should include these additional qualitative assessments methods (Furhauser et al., 2005; Meijer et al., 2005; Annibali et al., 2009; Belser et al., 2009). The importance of these additional parameters was outlined by (Pjetursson et al., 2007), who indicated that 38.7% of all implant-supported prosthetic restorations were associated with soft tissue complications.

Inconsistencies in implant outcomes were also observed, when studies were evaluated using different assessment criteria. This variability emphasised the need for a common approach to implant assessment and demonstrated why the lack of a universal set of criteria, was an obstacle to comparing different ARP techniques and surgical protocols (Donos et al., 2008). Differences in the standardisation and timings of x-rays was a specific concern, as it influenced the pictural depiction and measurement of the bone loss around the implant and consequently the implant survival status. Whilst several different implant assessment criteria have been proposed, the conditions described by Ong et al. (2008) appeared to be an effective method for the assessment of the implant/bone interface and the peri-implant conditions.

The outcome of placing an implant into a previously augmented site, did not appear to affect implant success or precipitate peri-implant bone loss at 12 months. The 100% implant success rate described, was analogous to the findings by Barone et al. (2012) and Ramanauskaite et al. (2019). The level of proximal bone loss at 12 months was observed to be small, with the average marginal bone loss ranging between 0.12 ± 0.4mm and 1.4 ± 0.9 mm in the GBR group, and 0.11 ± 0.1 mm to 1.28 ± 0.3 mm in the socket grafting group. Limited data was available for implant outcomes in sites treated with SS procedures.

12.3 Hard and soft tissue changes following alveolar ridge preservation

Whilst the application of ARP techniques, aims to optimise bone and mucosal tissue preservation during socket healing, the surgical protocol has been associated with complex flap manipulation, placement of an occluding membrane or matrix and grafting of the socket. (Horváth et al., 2013, Avila-Ortiz et al., 2019). The cumulative effect of these procedures may result in undesirable complications during the early stages of healing (Landsberg, 2008), affecting the bone and soft tissue topographical contour and differences in the quality and quantity of the regenerated bone and gingival tissue.

The second Systematic Review (Chapter 3) replicated the original approach of the first study, again asking two Focused Questions. The first Focused Question evaluated the effects of alveolar ridge preservation on bone linear and volumetric site dimensions, keratinised tissue measurements, histological characteristics and patient-based outcomes, when ARP was compared to unassisted socket healing. The second Focused Question examined the size effect of these outcomes, when undertaking GBR, SS and socket seal techniques. The risk for bias was unclear or high in most of the studies. Analysis indicated that ARP was associated with less mid-buccal vertical alveolar bone resorption, when compared to unassisted socket healing. The standardised mean difference (SMD) in vertical mid-buccal bone height between ARP and a non-treated site was 0.739mm (95% CI: 0.332 to 1.147) ($P<0.05$).

A lower level of horizontal bone resorption was found with ARP techniques, when they were compared with unassisted healing, but no statistically significant difference was observed when comparing results. Marked heterogeneity was seen in the horizontal dimensional change, with a -1.45 mm (95% CI: -1.892 to -1.008) reduction found for GBR and a -1.613 mm (95% CI: -1.989 to -1.238) reduction for socket grafting procedures. The heterogeneity was attributed to differences in the root shape, bone measurement position, measurement technique and bone phenotype (Tsigarida et al., 2020). The lack of consistency and standardisation in radiographic interpretation and research methodology, was also considered as contributing to the variation in the results. The advantage of using a barrier membrane with the ARP technique was inconclusive, but a greater vertical and horizontal bone conservancy was recorded with GBR, when compared with SS.

Analysis of the healed socket revealed an increased bone content in the ARP groups, with GBR studies reporting a total bone formation of 47.9 ± 9.1% to 24.67 ±15.92%. Significant variation was present in the treatment protocols and grafting materials used in the ARP studies, meaning it was difficult to predict the effect of a specific surgical technique with an individual graft. The percentage of new bone formation was also influenced by the presence of residual graft matrix and was dependant on the timing of bone healing. Adverse events were routinely reported with both unassisted socket healing and ARP procedures. ARP was associated with an increased frequency of oedema, facial pain and erythema. Few studies reported on variables associated with the patient experience in the ARP test or control groups. Outcome measures describing the gingival phenotype were not commonly reported, with limited data available on the effectiveness of the SS techniques.

12.4 Analysis of systematic reviews

Analysis of the two systematic reviews revealed that there was limited evidence to support the clinical benefit of ARP over unassisted socket healing, when considering implant outcomes. Whilst implant placement feasibility was similar in both the ARP and unassisted healing groups, the ability to adopt a prosthetically based protocol and the requirement for additional augmentation at fixture placement was unclear. The effect of ARP on the composition of the bone at the augmented site was undefined, with the consequence of using an ARP technique with a barrier membrane or matrix unspecified.

The results also indicated that the radiographic dimensional changes following ARP were varied, with no strong evidence to identify a superior ARP intervention (GBR or SS), when examining bone contour changes at 4 months healing. SS dimensional outcomes, or a direct comparison between GBR and SS ARP techniques required further investigation. This research should be designed to review the gingival phenotype, bone morphology and bone and soft tissue contour, with patient-based outcome measures included.

These outstanding questions were addressed by the design of a new RCT, which acted to compare GBR and SS ARP techniques against unassisted healing. The RCT was devised to have both primary and secondary outcomes measures.

The primary outcome measure recorded the radiographic dimensional changes of the extraction socket and alveolar ridge, using a new CBCT superimposition process. The secondary outcomes included the measurement of soft tissue contour changes using a unique CBCT and optical profilometric fusion methodology and an appraisal of the gingival phenotype. Advanced XMT radiographic imaging and a newly created computer analysis programme, assisted in determining the histological and osseointegration characteristics of the socket at 4 months healing. The secondary outcome measures also included an investigation into whether ARP influenced implant survival, augmentation requirements at implant placement and the patient-based healing experience.

12.5 Dimensional changes of the alveolar ridge and implant outcomes

The RCT described in Chapter 4, utilised a new radiographic assessment methodology, to assess socket healing dimensional changes. Whilst other researchers are now beginning to exploit the ability to superimpose and align CBCT images (Sapata et al., 2020, Sapata et al., 2019), this methodology enabled the superimposition and alignment of two CBCT different radiographs taken over a pre-determined period, affording the operator an opportunity to directly compare and reference small bone modelling changes. The technique attempted to eliminate chronological measurement bias, where researchers used either per-extraction CBCT images, or intra-oral radiographs of the transformed and partially healed socket, to calculate dimensional change.

The use of bone density to determine the edge of the bone margin was also unique and allowed the operator to identify the edge of newly forming alveolar tissue. This immature bone margin would not

normally be readily visible in the CBCT image, due to incomplete mineralisation. The technique offered a more sensitive method of determining bone changes, although the CBCT measurement was restricted by the sampling interval, and the voxel size of the reconstructed image.

Use of this radiographic fusion technique indicated that SS and GBR ARP procedures were associated with effective conservancy of the alveolar bone height ($p=0.02$ and $p = 0.007$), in the mid-buccal and mid-palatal margins of the socket. The buccal BARH increase of 0.07mm (SD 0.83) following GBR was considered clinically significant, as it demonstrated conservancy of buccal bone dimension, when compared to the -0.52mm (SD 0.8) loss recorded in association with unassisted socket healing ($p=0.007$). The vertical ridge conservancy offered with GBR and SS could have a positive impact on implant placement, aesthetic outcomes, and may reduce augmentation requirements reducing surgical treatment costs.

The mid-socket coronal width change was similar for the ARP and Control test groups (26-27%). The horizontal reduction was higher than the predicted effect size from the Systematic Review in Chapter 3 and lower than the observed results from the systematic reviews by Ten Heggeler et al. (2011) and Van der Weijden et al. (2009). The results of this RCT appear to agree with the systematic review by Couso-Queiruga et al. (2021), who indicated that ARP had a variable effect at preserving the horizontal ridge dimensions in the coronal aspect. The area measurements recorded comparative levels of cross-sectional alveolar bone loss (6-11%), with only two patients in the study retained the top 3mm of the buccal socket wall. Both cases were observed to have a socket thickness of above 1.5mm, strengthening the understanding that bone thickness acted as a predictor for buccal bone resorption (Chappuis et al., 2017, Avila-Ortiz et al., 2020a, Araújo et al., 2015, Araujo and Lindhe, 2005, Tomasi et al., 2010).

GBR was observed to be more predictable at preserving the coronal buccal width. This finding corresponded with the outcome of the systematic review by Avila-Ortiz et al. (2019), who indicated that ARP using a xenogenic graft covered with an absorbable collagen membrane, or a rapidly absorbable collagen sponge, produced the most favourable outcome in terms of horizontal ridge preservation. Whilst variation in the horizontal measurement position may account for some of dimensional difference observed in the studies, it was postulated that the use of a GBR technique offered advantages. Extension of the GBR membrane onto the peripheral bone surface, acted to improve the stability of the membrane and reinforce its barrier integrity. The systematic review by Bassir et al. (2018) also observed that barrier membrane integrity influenced alveolar ridge width conservancy, suggesting that early barrier failure adversely affected bone healing outcomes.

Whilst minor differences were observed in tissue healing and early pain experience, this study indicated that ARP was not associated with adverse patient outcomes. Postoperative complications were common following ARP and Control groups, with breakdown of the collagen membrane observed in 28% of GBR patients and failure of the matrix detected in 43% of SS cases. The breakdown of the barrier

integrity predominantly occurred in the proximal areas, with graft sequestration more common with the SS technique. Pain scores were similar in all three test groups at 2 weeks healing.
In summary, both GBR and SS ARP were effective at preserving the vertical alveolar bone height, when compared to the control, but proved less effective at maintaining the horizontal bone contour. The adoption of an ARP technique was not associated with prolonged patient discomfort.

12.6 Soft tissue contours

The aesthetic outcome of implants placed in the anterior maxilla is challenging, with the height of the lip line and the extent of the gingival display, affecting the visibility and profile of the patients smile. Any inconsistencies in the symmetry and configuration of the soft tissue and prosthetic structure will be visible and will affect the patient's perception of success (Belser et al., 2004). The achievement of an acceptable aesthetic outcome is also dependent on establishing a stable mucosal structure, with an optimal mucosal keratinised tissue width and thickness (Chappuis et al., 2017, Chappuis et al., 2015, Belser et al., 2004). This mucosal stability will support the establishment of a stable peri-implant phenotype (Avila-Ortiz et al., 2020a), with an adequate zone of peri-implant tissue being essential to minimise the risks of future peri-implant disease (De Risi et al., 2015).

Chapter 7, sought to investigate soft tissue contour changes, following ARP using GBR and SS techniques, in comparison with unassisted healing. The results indicated that GBR was associated with a statically significant ($p=0.02$) reduction in the Mid-buccal cervical contour change (-1.65mm±0.69) when compared with the SS and Control groups, at both 8 weeks and 4 months healing. A statistical significance was also found when comparing the vertical contour change following GBR against SS and Control groups, at both 8 weeks ($p=0.014$) and 4 months ($p=0.026$) healing. Whilst differences in the magnitude of the contour reduction was present when using different ARP techniques, the extent of coverage of the buccal and palatal tissue recontouring, was similar for both ARP and the Control.

This study used a new superimposition technique, that combined two optical profilometric scans, or a profilometric scan and a CBCT images, to assess soft tissue contour changes and mucosal tissue thickness. Whilst the technique was unique at instigation of the study, a similar methodology has now been reported by Jonker et al. (2021) and Sapata et al. (2020). The adoption of this particular methodology and the ability to examine and codify specific contour changes, at a particular location, is an important tool for researchers. Particularly as it allows for visual comparison of the complete topographical contour, elucidating more specific tissue changes. This greater accuracy will ensure that acknowledgement is given to results where soft tissue expansion has compensated for alveolar bone loss. Additional knowledge on the magnitude of ARP soft tissue and mucosal transformation, will advance and complement reporting based on aesthetic outcomes.

As the DBBM graft was consistent in both the GBR and SS ARP techniques and the mucosal phenotype was thick in all test groups, the superiority of GBR in retaining the soft tissue contour would again

appear to be associated with the GBR membrane providing a more stable foundation for bone and mucosal development. The potential for the GBR ARP technique to cause soft tissue recession as a result of raising a tissue flap was not realised, as papilla recession was comparable in all test groups. This preservation of the soft tissue contour and the mucosal configuration, may have advantages in improving future patient based aesthetic outcomes (Noelken et al., 2018, Avila-Ortiz et al., 2014a, Araujo et al., 2015, Thoma et al., 2009)

Soft tissue contour is co-dependent on alveolar bone structure and mucosal volume and composition, to define the 3D topographical profile outline. As bone resorption is inevitable during socket healing, a compensatory expansion of the mucosal volume (Thoma et al., 2020b, Chappuis et al., 2015) may be responsible for influencing the healed shape and dimensional changes seen at the edentulous site. This new methodology ensured that the contribution of each tissue compartment to contour change was acknowledged.

The effect of the periodontal phenotype was also taken into consideration in designing this study, as the inclusion criteria limited enrolment to those patients with a thick flat or scalloped phenotype. This prerequisite restricted the potential for compensatory development of the mucosal volume seen in thin phenotypes (Chappuis et al. 2015), with the relationship between a thick gingival phenotype and post-surgery tissue stability confirmed by the limited keratinised tissue and mucosal thickness changes reported in the ARP test groups and the Control.

In summary, the results in Chapter 8 suggest that ARP using the SS principle, did not appear to offer a clinical advantage over the Control, when tissue contour changes were assessed. Whilst it has been previously acknowledged that dimensional changes can be influenced by the specific ARP collagen matrix and the surgical technique (Atieh et al., 2012, Burch, 2021, Atieh et al., 2021), the results indicated that the GBR technique and membrane placement was more effective at preserving the soft tissue contour.

12.7 Histological assessment of bone healing

One of the principal objectives for ARP, is to promote physiological healing and new bone development in the extraction socket. Various biomaterials and ARP technical approaches have been advocated, with limited evidence available to support the superiority of a specific ARP technique, when considering new bone formation within the healing socket area. The findings from the systematic review in Chapter 3, indicated significant heterogeneity in the histological composition of the healed socket, with the systematic review by Majzoub et al. (2019) advocating that further research was required to directly compare the outcome of specific ARP graft materials. Consequently, the literature remains inconclusive regarding the ideal ARP surgical technique and biomaterial necessary to promote socket healing.

Chapter 9 was designed to investigate the histological bone composition of trephined bone samples, following GBR and SS ARP techniques. The surgical techniques examined the impact of using a GBR membrane, against a SS with a collagen matrix, in conjunction with a DBBM graft material. Unassisted healing acted as the Control.

BSE-SEM image analysis demonstrated a statistically significant difference ($P<0.005$) in the percentage area of new bone formation in the Control (45.89%), when compared to GBR (22.12 %) and SS (27.62 % SD) ARP test groups. The percentage area of connective tissue and residual DBBM graft in the GBR (28.17%) and SS (24.37%) groups was comparable. No evidence of active remodelling of the DBBM graft matrix was seen from the BSE-SEM iodine sublimation process in either the GBR or SS ARP groups at 4 months healing.

The percentage bone volume from the XMT analysis, was found to be lower than that of the BSE-SEM area findings. XMT analysis found that the percentage volume of new bone formation was higher in the Control group (44.43%), when compared to GBR (21.27%) and SS (19.83%) techniques, with the volume of residual graft matrix greater with GBR (25.4%), when compared to SS (18.29%). This difference being accounted for by the higher level of graft sequestration found with the SS technique and reported in Chapter 6. The reduced new bone formation in the GBR and SS ARP procedures, appeared to have been affected by the retention of the residual graft, which limited the space available for new bone formation. A greater level of graft-bone osseointegration was found with GBR (35.66%) when compared to SS (31.18%).

The ability of ARP techniques to promote new bone formation through an osteoconductive approach has been described in several studies (Barone et al., 2008, Cardaropoli and Cardaropoli, 2008) and in the systematic review by De Risi et al., (2013), Horváth et al., (2013) and Canellas et al., (2020). The choice of bone substitute material is often dependant on the preference of the clinician, patient funding, or cultural background, with the use of a DBBM matrix validated in longitudinal ARP studies (Barone et al., 2013b, Heberer et al., 2011, Pang et al., 2017) and the systematic review by Chan et al. (2013). Whilst the percentage of new bone formation with DBBM has been observed to be variable, the results from this study demonstrated that when DBBM was used (GBR or SS), it resulted in a decrease in new bone formation, with this percentage lower than that reported in other studies (Cook and Mealey, 2013, Perelman-Karmon et al., 2012, Gholami et al., 2012). The difference in results may be attributed to the highly detailed nature of the imaging and analysis process undertaken, or as a result of variation in the length of the healing period and the bone sample site chosen (Ayna et al., 2015, Testori et al., 2013, Riachi et al., 2012). The design and use of an innovative and unique image analysis protocol offered several advantages in this study, as it allowed for the evaluation of both the area and volume of new bone formation in the bone core sample. It offered both a highly detailed qualitative assessment of the bone core sample, with the XMT analysis allowing digital image reconstruction of the core in any orthogonal view. This method effectively reduces the risk of selection bias, when compared to the

analysis of a single planar view under light microscopy. The ability to differentiate between the apical and coronal segments of the bone sample was also innovative, permitting a more detailed analysis of the healing pattern within the extraction socket. The use of a volume rendering STL image reconstruction of the XMT data set, facilitated a more accurate and detailed visualisation of the socket healing process, with the iodine sublimation process providing detailed visualised of the cellular response during healing.

Impact of Residual Graft Material in (Histological) Bone Healing: This study confirmed the association between the presence of residual DBBM graft, with a lower level of new bone formation (Heberer et al., 2011, Park et al., 2010, Nam et al., 2011). It also suggested that the retained DBBM matrix was related to a delay in bone regeneration and remodelling response (Heberer et al., 2011, Geurs et al., 2014, Lindhe et al., 2014). Whilst visual evidence of osteoclastic multi-nucleated cell activity was not observed on the residual graft matrix in this study, osteoclasts have been observed by others (Hämmerle et al., 1998, Hämmerle et al., 1997, Tapety et al., 2004), potentially indicating that graft resorption does eventually occur, allowing eventual replacement of the scaffold. It might be argued that longer healing periods could improve histological outcomes, due to increased bone formation, however Chapter 2 indicated that comparable survival and success rates could be achieved when implants were placed at different healing periods. The systematic review by De Risi et al., (2013) suggesting that implant placement could be successfully performed after 3 or 4 months of healing, independent of the grafting materials used.

***Impact of APR technique in histological bone healing*:** The ARP surgical technique appeared to influence bone formation, with a higher level of new bone observed with the GBR technique. Whilst the GBR procedure is associated with minor flap elevation and a more complicated surgical process, this more invasive approach was not a disadvantage when compared against the SS flapless procedure. The integrity of the GBR membrane appears to be more effective than the SS technique, in the open membrane ARP approach, enabling greater osteoconduction and bone formation (Sculean et al., 2019, Retzepi and Donos, 2010). The SS technique was accociated with a higher level of matrix breakdown, increased instability of the graft matrix, a higher risk of graft sequestration and less bone formation. The reduced bone formation affecting the level of osseointegration between the new bone and the DBBBM particles and increasing the amount of their fibrous encapsulation seen in the coronal aspect of the bone sample.

Histologically, fibrous encapsulation of the graft matrix was seen in all the GBR and SS bone samples. This observstion is at odds with the findings of the systematic review in Chapter 3, which indicated that only three of the twenty-four included studies reported graft encapsulation (Cook and Mealey 2013, Lindhe et al., 2014 and Mardas et al., 2010). Evaluation of the BSE-SEM and XMT images indicated

that when the membrane or matrix remained intact, a centralized area of coronal fibrous graft encapsulation was formed, with bone development noted in the peripheral areas of the sample. When membrane integrity failed, no bone formation was seen in this area. This healing characteristics was witnessed by Carmagnola et al. (2003).

The breakdown rate of both the GBR and SS collagen materials was advanced in this study, due to the adoption of an "open healing" ARP approach. Whilst the improved substantivity of the GBR membrane accounted for differences in new bone formation, when compared to SS techniques, early breakdown of the collagen membrane and matrix in both groups, resulted in fibrous tissue formation and encapsulation of the graft matrix. Since successful regeneration is obtained only when cell occlusion and space is maintained, allowing adequate time for the bone progenitor cells to repopulate the defect, the requirement for a long-lasting ARP membranes or matrix needs to be reviewed (Mardas et al., 2010, Calciolari et al., 2018b).

The use of more substantive membrane has been considered by several researchers, with proposals including the use of a double collagen membrane layer (Choi et al., 2017, Buser et al., 2004), d-PTFE membranes (Sun et al., 2019), polypropylene barriers (Dos Santos et al., 2021), titanium meshes (Sagheb et al., 2017) and reinforced cross-linked collagen membranes (Guarnieri et al., 2015). The recent systematic review by Canullo et al. (2021) reported on the viability of using a cross-linked collagen membrane in combination with an autogenous graft in ARP procedures. Unfortunately, this outcome needs to be treated with caution, as a high risk of reporting bias was found in the included studies. Future research studies should consider the substantivity and graft resorption patterns of ARP materials, to determine if they offer a clinician advantage.

12.8 Implant success and survival, and augmentation requirement

The RCT in Chapter 11, indicated that implant survival was 100% in the GBR, SS and Control groups at loading, with two patients in the SS and one in the Control groups observed as suffering proximal bone loss. Disparities were present when the proximal bone changes were related to implant outcomes measures, highlighting the need for a common approach to assessment implant success in ARP studies. Whilst all patients were able to realise implant placement in a prosthetically orientated position, ARP cases required less augmentation at fixture placement (Avila-Ortiz et al., 2019; Lim et al., 2020; Thoma et al., 2020). GBR had a reduced augmentation requirement when compared to SS. ARP did not appear to influence implant success, or implant survival characteristics. GBR appeared to offer both an operative and clinical advantage to SS, when considering the requirement for bone augmentation at implant placement. The thick biotype required for inclusion in this study, may also have affect the implant augmentation requirements, as a thicker bone morphotype would result in less buccal bone loss and improve the residual bone morphology in both the ARP test groups and the Control groups.

12.9 Concluding remarks

From this series of projects, the following conclusions can be drawn:

- ARP (GBR and SS) resulted in a reduction in the vertical alveolar bone dimensional change, following tooth extraction.
- ARP (GBR and SS) procedures were associated with a decreased need for ridge augmentation during implant placement. GBR was more effective at facilitating implant placement, due to its reduced Mid-SA bone loss.
- GBR was clinically more effective at preserving the horizontal buccal bone dimensions and soft tissue contour, when compared to SS and unassisted socket healing.
- A SS ARP technique using DBBM and a collagen matrix, offered little if any advantage in preserving the vertical and horizontal contour changes and mucosal characteristics, when compared to unassisted healing.
- Unassisted healing resulted in more new bone formation (area and volume) than GBR and SS procedures but was associated with a loss of soft tissue contour and a reduction of vertical bone height. Careful case selection and surgical planning is required to gain the full benefit of the ARP procedure.
- GBR and SS ARP procedures produced similar levels of new bone formation, but GBR was associated with more osseointegration between the DBBM graft and new bone.
- The new bone formation was confined to the middle and apical areas of the healed socket. Coronally bone was found in the peripheral margin of the bone core, only when the GBR and SS occluding barrier remained intact.
- Fibrous encapsulation of the graft was associated with early breakdown of the barrier seal in both GBR and SS ARP groups.
- Exposure of the collagen barrier and matrix to the oral environment (open membrane technique), may have influenced the compartmentalisation of the healing socket tissue, affecting regenerative cellular pathways and inflammatory processes.
- XMT analysis was effective at calculating the histological composition of the bone sample.
- Fused optical and CBCT images, were an effective method of assessing soft tissue contour change.
- Referenced and aligned CBCT images, offered an advantage when reviewing bone dimensional changes.
- Implant success and survival rates were similar for the ARP test groups and the Control.

12.10 Future research directions

The results from this thesis indicate that there is still a need for high quality RCTs, based on adequately powered sample sizes, to evaluate differences in implant related outcomes, when comparing different ARP procedures and specific surgical protocols, against unassisted socket healing. Radiographic and contour outcomes associated with SS ARP procedures, require additional comparative studies. The role of possible confounding factors like smoking, reason for extraction, tooth type and location, integrity of buccal bone plate, flap reflection and primary tissue closure, should also be investigated.

Future trials should place an emphasis on:

a) Decreasing the risk of study heterogeneity, whilst controlling previously reported sources of reporting bias.
b) Undertaking an RCT with a higher population size and power, to assess whether a statistically significant difference in horizontal bone and soft tissue contour changes is present when comparing ARP with unassisted healing.
c) Assessing the need for site augmentation and implant placement feasibility, when considered against the aspiration of a prosthetically driven implant placement protocol and standardised implant size selection.
d) Evaluating the survival and success of implant placement in at an ARP site, when using a standardised and universally accepted set of criteria.
e) Investigating the use of slower resorbing barrier membranes and their effect on new bone formation.
f) Analysis of the effects of using resorbable ARP graft particles, which promote new bone formation, whilst facilitating soft tissue regeneration.
g) Radiographic assessment of implant marginal bone levels, using standardised radiographs taken over specific evaluation periods. Key radiographic evaluation stages should include post implant placement, implant loading and one year after loading.
h) Appraising white and pink aesthetic scores for implant supported restorations following ARP procedures. The patient-based outcomes should include a cost benefit analysis for different procedures.
i) Evaluation of soft tissue topographical dimensional changes, using 3D computer aided analysis.
j) The use of BSE-SEM and XMT qualitative bone analysis and the developed image interpretation software, to evaluate the percentage of new bone formation following ARP procedures.

Chapter 13

APPENDIX

13.1 Details of collaboration and publications

MARDAS, N., TRULLENQUE-ERIKSSON, A., MACBETH, N., PETRIE, A. & DONOS, N. 2015. Does ridge preservation following tooth extraction improve implant treatment outcomes: a systematic review: Group 4: Therapeutic concepts & methods. *Clin Oral Implants Res,* 26 Suppl 11**,** 180-201.

MACBETH, N. 2016. An audit of case Referral Complexity at the CRD Department. *In:* DENTISTRY, C. F. R. (ed.). HQ DPHC Lichfield: Surgeon Generals Department.

MACBETH, N., TRULLENQUE-ERIKSSON, A., DONOS, N. & MARDAS, N. 2016. Hard and soft tissue changes following alveolar ridge preservation: A systematic review. *Clin Oral Implants Res*, 28(8), 982-12911.

COMBES, J., PEPPER, T., BRYCE, G. & MACBETH, N. 2018. Dental care provision to UK military personnel serving on Operation Herrick in Afghanistan. Part 1: access to dental care. *Br Dent J,* 225**,** 1068-1072.

BRYCE, G., DIESSNER, N., HEMMINGS, K. & MACBETH, N. 2019. Solutions for implants placed with prosthetic inconvenience. *Dental Update,* 46**,** 1003-1014.

COMBES, J., PEPPER, T., BRYCE, G. & MACBETH, N. 2019. Dental care provision to UK military personnel serving on Operation Herrick in Afghanistan. Part 2: aetiology and management. *Br Dent J,* 226**,** 50-54.

MACBETH, N., STERLITZ, S. & BRYCE, G. 2019. Amlodipine-induced gingival overgrowth in the peri-implant region: A review and case report. *Dental Update,* 46**,** 280-284.

MACBETH, N., DONOS, N. 2021. Treatment of Peri-implant mucositis and abutment level sinus in the Aesthetic Zone. *ITI Treatment Guide – Volume 12:* USA. Quintessence publication, Chap 6.

13.2 List of posters

MacBeth N., Mardas N., Donos, N., Post Extraction Soft and Hard Tissue Changes Following Ridge Preservation. British Society of Restorative Dentistry Conference. Feb 21.

MacBeth, N., Mardas, N., Donos N., Boyde A. Post extraction Soft and Hard Tissue Changes Following Tissue Preservation Procedures. 2017 EuroPerio 9, Amsterdam.

13.3 List of Oral Posters

MacBeth N, Donos, N. Post-Extraction Radiographic and Gingival Changes Following Alveolar Ridge Preservation- Poster 1299. Ten-minute poster presentation IADR/AADR/CADR General Session and Exhibition. July 21- 24, 2021. Virtual Experience.

13.4 Presentations

Restoration of the failed dentition. BSSPD lecture at the PanDental Society Conference. 2017.

The Case for alveolar ridge preservation Pan London STR conference 2017

Periodontal Surgery and Treatment Planning Decision for The Practitioner. MSc Periodontal programme. Peninsular University. 2017, 18, 19 20 and 21.

Periodontal crown lengthening lecture and hands on course. MSc Periodontal programme. Peninsular University. 2017, 18, 19 20 and 21.

Defence Primary Health Care Dental Webinar Alveolar Ridge Preservation. 2019 and 2021.

Treatment Planning for the Traumatised Dentition- Lecture and hands on training course. Defence Primary Health Care Dental. 2020 and 2021

Manchester University and FGDP and CGDent lecturer and prosthodontic training lead for FGGDP/ CGDent Diplo and Msc Restorative programmes.

13.5 Research Grants

October 2015: Defence Medical Academy/ Centre for Aviation and Medicine: £9,000 PhD Research costs. Apr 2016, Henlow, UK.

January 2018: Military of Defence Research Institute: £12,000 for histology and XMT imaging of bone particles. PhD Research Funding Submission. Jan 2018 QMUL, London, UK.

APPENDIX A

PARTICIPANT INFORMATION SHEET

Study title

An evaluation of post extraction alveolar bone morphology following tissue preservation procedures.

Invitation to take part

You have been invited to join this study, as you have suffered damage to a tooth, which cannot be restored by conventional dental treatment.

The opportunity of replacing the damaged tooth with an implant-supported restoration has been discussed as a component of your treatment. Following your initial assessment, it was noted that the bone levels around the affected tooth, was insufficient to allow direct placement of a dental implant. The adoption of a tissue preservation procedure; following extraction of the tooth; may allow the retention of the bone tissue in tooth socket area and help to simplify subsequent implant treatment. This is because the procedure may reduce the requirement for further bone grafting and allow placement of the implant in a more favourable position.

What is the purpose of the research?

This is an original clinical research project, to evaluate the ability of three different alveolar ridge preservation techniques, to promote bone healing and the retention of soft tissue volume, following the extraction of a tooth. The 3 procedures will be assessed by clinical radiographic and histological characteristics.

Who is doing this research?

All the prosthetic and surgical treatment will be undertaken by Wg Cdr N Macbeth, the Consultant in Restorative Dentistry, at the Centre for Restorative Dentistry (CRD) in Aldershot.

Why have I been invited to take part?

The tooth indicated for extraction, has been assessed as having a reduced bone volume around its root. This is because localised infection may have led to resorption of the adjacent tissue, or the original bone layer was very thin at this site.

Following extraction of your tooth, the initial healing processes can result in further bone and tissue remodelling at this site. This can result in up to 3.7mm of shrinkage of the local tissues. Bone preservations procedures try to reduce the level of tissue remodelling and ensure that sufficient bone tissue remains to allow implant placement at the affected site. The preservation of the bone tissue will act to simplify the subsequent implant procedure and reduce the complexity of the treatment. The retention of the tissue will also act to improve the aesthetics of the final restoration provided.

Do I have to take part?

You are under no obligation to take part in this study. Alternative prosthetic treatment can be discussed and offered as an alternative within the CRD department. The availability of an implant-supported restoration would not be affected by this decision, but your suitability for this treatment would need to be re-assessed following the initial healing period.

What will I be asked to do?

You will be asked to attend the dental clinic on 10 separate visits, over a 12-month period, to allow assessment, surgical management and prosthetic restoration of the failing tooth. Clinical, radiographic and histological measurements will be recorded as a component of these examinations.

What is the device or procedure that is being tested?

The ability of individual collagen or bone substitute materials to preserve the alveolar bone, following extraction of a tooth.

What are the benefits of taking part?

Preservation of the bone volume may help to facilitate later implant placement, as it will reduce the rate of bone resorption, may promote new bone development, prevent shrinkage of the bone height and width, allow more favourable implant placement and reduce the requirement for further complex bone augmentation procedures.

The graft materials used in the study have also been suggested as a method to encourage bone healing and to extend the time frame for treatment. This is particularly important if operational deployment or training commitments prevent access for care within the military environment.

What are the possible disadvantages and risks of taking part?

Although the treatment will require that a slightly more complex surgical procedure is adopted, when the tooth is extracted, it should not increase the likely hood of infection or tissue shrinkage at the extraction site. If breakdown of the graft site does occur, the healing process in the bone tissue should progress in an unaffected way, but the site may require further bone augmentation procedures if implant treatment is pursued.

It is important that you are aware that that implant fixtures have a 2 -5% risk of early failure, due to a lack of osseointegration at the bone site. This may be associated with your medical history or social factors (past smoking habits).

The provision of an implant-supported restoration also requires that a regular maintenance programme is established with your dentist, to ensure that the health of the gingival and alveolar bone tissues is maintained.

Since implant treatment is often two or three times more expensive than other more traditional options, you should be aware of the ongoing upkeeps costs if you leave the military.

Can I withdraw from the research and what will happen if I don't want to carry on?

Yes, you can withdraw at any time, with your treatment continued according to the original treatment plan.

Are there any expenses and payments which I will get?

There are no payments or expenses provided for participation in this project.

Will my taking part or not taking part affect my Service career or medical care?

Participation in this study should not affect your Service Career or medical care in any way.

Whom do I contact if I have any questions or a complaint?

If you have any questions or concerns relating to this study, you can contact clinical staff within the CRD department or the practice manager Sgt Claire Danby (MOD Tel: 94222 2895, BT: 01252 347895)

What happens if I suffer any harm?

All direct surgical interventions have a risk of physical tissue damage. This may manifest as pain, inflammation and swelling, with local tissue recession, remodelling and adjacent tooth sensitivity resulting as a consequence. Although these inherent risks are anticipated as part of the interventional procedure, they will not be considered as adverse risk event in the context of this study.

What will happen to any samples I give?

All study documentation (forms, investigators files, patient radiographs and photographs) will be kept at the CRD department after the study is completed for at least 11 years and the Investigator(s) should be available during this time to answer any queries associated with the study. These records will then be archived according to Defence Dental Services archive procedures.

Histology samples will be sent to an external lab for analysis, but all patient details will be anonymised, with the samples returned to the CRD department upon completion of treatment.

Will my records be kept confidential?

All clinical records specific to the clinical study will be anonymised and stored in the CRD department.

Initial consultation records, letters of correspondence and digital X-rays will be added to your normal electronic medical recorded as detailed by the Defence Dental Service policy documents.

Originals of the study clinical data forms, casts or other items and originals of the study records shall be stored in a secured location within the CRD department. A digital back up of recorded digital x-ray images will be saved on an external hard drive and positioned in a fire-poof safe at the end of every session.

You will be provided with a letter with full disclosure of the medical devices utilised during your care at the completion of treatment.

Who is organising and funding the research?

This study has been sponsored by the Surgeon Generals Research Strategy Group for the costs of

the programme and the histological analysis of the alveolar bone samples.

The Defence Dental Service has agreed to provide funding for the clinical and surgical components of this study.

The analysis of the alveolar and gingival tissue grafting procedures; using the CAD / CAM Nobel Procera system has been supported by the American division of the Nobel-Biocare implant company.

Who has reviewed the study?

This study has been reviewed and given favourable opinion by the Ministry of Defence Research Ethics Committee (MoDREC).

Further information and contact details.

Sgt Claire Danby, Practice manager, CRD Department, DDS Aldershot, Evelyn Woods Road, Aldershot. GU11 2LS. MOD Tel: 94222 2895, BT: 01252 347895.

Compliance with the Declaration of Helsinki.

This study complies, and at all times will comply, with the Declaration of Helsinki[1] as adopted at the 64th WMA General Assembly at Fortaleza, Brazil in October 2013.

[1] World Medical Association Declaration of Helsinki [revised October 2013]. Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects. 64th WMA General Assembly, Fortaleza (Brazil).

Appendix B

CONSENT FORM FOR PARTICIPANTS IN RESEARCH STUDIES

Title of Study: An Evaluation of Post Extraction Alveolar Bone Morphology and Gingival Tissue Contour Following Tissue Preservation Procedures

Ministry of Defence Research Ethics Committee Reference:

- ☐ The nature aims and risks of the research have been explained to me. I have read and understood the Information for Participants and understand what is expected of me. All my questions have been answered fully to my satisfaction.
- ☐ I understand that if I decide at any time during the research that I no longer wish to participate in this project, I can notify the researchers involved and be withdrawn from it immediately without having to give a reason. I also understand that I may be withdrawn from it at any time, and that in neither case will this be held against me in subsequent dealings with the Ministry of Defence.
- ☐ I understand that the screening process to decide if I am suitable to be selected as a participant may include completing a medical screening questionnaire and/or a physical examination by a Dental officer and I consent to this.
- ☐ I consent to the processing of my personal information for the purposes of this research study. I understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.
- ☐ I agree to volunteer as a participant for the study described in the information sheet and give full consent.
- ☐ This consent is specific to the particular study described in the Information for Participants attached and shall not be taken to imply my consent to participate in any subsequent study or deviation from that detailed here.
- ☐ I understand that in the event of my sustaining injury, illness or death as a direct result of participating as a volunteer in Ministry of Defence research, I or my dependants may enter a claim with the Ministry of Defence for compensation under the provisions of the no-fault compensation scheme, details of which are attached.

Participant's Statement:

I _____

agree that the research project named above has been explained to me to my satisfaction and I agree to take part in the study. I have read both the notes written above and the Participant Information Sheet about the project, and understand what the research study involves.

SIGNED DATE

Witness **Name**

Signature

Investigator's Statement:

I _____

confirm that I have carefully explained the nature, demands and any foreseeable risks (where applicable) of the proposed research to the Participant.

Signed Date

AUTHORISING SIGNATURES

The information supplied above is to the best of my knowledge and belief accurate. I clearly understand my obligations and the rights of research participants, particularly concerning recruitment of participants and obtaining valid consent.

Signature of Principal Investigator

…… **Date**

Name and contact details of Independent Medical Officer (if appropriate):

Name and contact details of Principal Investigator:
Wg Cdr N MacBETH, Centre for Restorative Dentistry, DDS Aldershot, Evelyn Woods Road, Guilford. GU11 2LS

ARRANGEMENTS FOR THE PAYMENT OF NO-FAULT COMPENSATION TO HUMAN VOLUNTEERS

1. This section sets out the arrangements for the payment of no-fault compensation to volunteers who suffer illness and/or personal injury as a direct result of participating as a non-patient (healthy) human volunteer in research conducted on behalf of the Ministry of Defence. The no-fault compensation arrangements only apply to volunteers (Military, Civilian, or non-Ministry of Defence) who participate in a Trial that has been approved by the MoD Research Ethics Committee.

2. A volunteer wishing to seek no-fault compensation under these arrangements should contact the Directorate of Judicial Engagement Policy, Common Law Claims & Policy (DJEP-CLCP) Ministry of Defence, Level 1, Spine 3, Zone J, Whitehall, SW1A 2SB who may need to ask the Claimant to be seen by a MoD medical adviser.

3. CLCP will consider reasonable requests for reimbursement of legal or other expenses incurred by volunteers in relation to pursuing their claim (e.g., private medical advice, clinical tests, legal advice on the level of compensation offered) provided that they have been notified of the Claimant's intention to make such a Claim.

4. If an injury is sufficiently serious to warrant an internal MoD inquiry, any settlement may be delayed at the request of the volunteer until the outcome is known and made available to the volunteer in order to inform his or her decision about whether to accept no-fault compensation or proceed with a common law claim. An interim payment pending any inquiry outcome may be made in cases of special need. It is the Claimant's responsibility to do all that he or she can to mitigate his or her loss.

5. In order to claim compensation under these no-fault arrangements, a volunteer must have sustained an illness and/or personal injury as a direct result of participation in a Trial. A claim must be submitted within three years of when the incident giving rise to the claim occurred, or, if symptoms develop at a later stage, within three years of such symptoms being medically documented.

6. The fact that a volunteer has been formally warned of possible injurious effects of the trial upon which a claim is subsequently based does not remove MoD's responsibility for payment of no-fault compensation. The level of compensation offered shall be determined by taking account of the level of compensation that a court would have awarded for the same injury, illness or death had it resulted from the Department's negligence.

7. In assessing the level of compensation, CLCP, in line with common law principles, will take into account the degree to which the Claimant may have been responsible for his or her injury or illness and a deduction may be made for contributory negligence accordingly.

8. In the event of CLCP and the injured party being unable to reach a mutually acceptable decision about compensation, the claim will be presented for arbitration to a nominated Queen's Counsel. CLCP will undertake to accept the outcome of any such arbitration. This does not affect in any way the rights of the injured party to withdraw from the negotiation and pursue his or her case as a common law claim through the Courts.

Appendix C

Appointment Schedule and data sheets

	VISIT NO.	DATE SCHEDULED	ACTUAL VISIT DATE
Enrolment Visit	1		
Extraction of Tooth Base Line Evaluation (+ 1 Day)	2		
Suture Removal and Post-Operative review (2 Weeks)	3		
Post-Operative review (8 Weeks)	4		
CBCT and Implant Placement (16 weeks)	5		
Post-Operative Review (18 Weeks)	6		
Second stage surgery (28 Weeks)	7		
Second Stage Surgery Review (30 Weeks)	8		
Implant Impression (36 Weeks)	9		
Restoration of Implant (40 Weeks)	10		
Six Month Follow-up (66 Weeks)	11		
12-month Follow-up (96 Weeks) Termination Visit	12		

Parameters		Tooth Extraction and ARP			Implant Placement – Healing time				Implant Restoration - Follow up			
	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9	VISIT 10	VISIT 11	Visit 12
	Enrolment Visit	Extraction of tooth	Suture removal	Post-op Visit	CBCT Implant Placement	Post Op Review	Second stage surgery	Post Op review	Implant Impression	Restoration of Implant	6 Month Follow-up	12 Month Follow up
	0	Baseline (+1)	2 Weeks	8 Weeks	16 Weeks	18 Weeks	24-28 Weeks	30 Weeks	36 Weeks	40 Weeks	66 Weeks	92 Weeks
Informed consent	X											
Incl. /Excl. criteria	X											
Med & Dent history	X											
Demographics	X											
Social History	X											
Patient Info Sheet	X											
Alginate Impression	X											
Measurement Stent	X	X										
Randomisation		X										
Letter to GDP	X											
Extraction of Tooth		X										
CBCT		X			X							
Clinical bone width		X			X							
Full mouth plaque score	X			X	X		X			X	X	X
Bite Index	X								X			
Impression taking	X	X			X				X		X	X
Standardized X-ray	X				X				X	X		X
PPD, REC, CAL, BOP		X		X	X		X		X	X	X	X
Keratinised Tissue		X		X	X		X		X	X	X	X
Intra-surgical hard & soft tissue measurements		X		X	X		X					
Implant placement					X							
Bone biopsy					X							
Provisional prosthesis/denture		X			X							
Pain evaluation		X	X	X	X	X	X	X	X	X	X	X
Suture removal			X			X		X				
Oral Hygiene Instruction/ prophylaxis			X	X	X		X	X	X	X	X	
Chlorhexidine rinsing		X	X	X			X					
Final prosthesis							X					
Lab form	X											
Implant success criteria												X
Implant survival						X	X	X	X	X	X	X
Intraoral photographs		X	X	X	X	X	X	X	X	X	X	X
Wound healing assessment			X	X		X		X				
OHIP 14		X					X		X	X	X	X
Pink Aesthetic Score (PES)										X	X	X
White Aesthetic score (WES)										X	X	X
Time Taken		X			X		X					
Adverse event / SAE		X	X	X	X	X	X	X	X	X	X	X
Concomitant drug therapy		X	X	X	X	X	X	X	X	X	X	X

PARTICIPANT INFORMATION SHEET (1)

Study title

An Assessment of Bone and Soft Tissue Contour Following Extraction of a Tooth.

Invitation to take part

You have been invited to take part in this study, as you have suffered damage to one of your natural teeth that cannot be repaired with normal dental treatment. Your dentist has suggested that this tooth needs to be removed (extracted), to return your mouth to a healthy state.

Several different methods of replacing the missing tooth have been discussed with you. These have included the manufacture of a removable denture, a bridge that is fixed to your adjacent teeth or a tooth supported on a dental implant. You have requested that an implant-supported replacement be provided.

Unfortunately, when a natural tooth is lost, shrinkage and remodelling of the bone occurs at the site where the tooth has been removed. This change is part of the normal healing process, but if severe can affect the ability of the dentist to place the implant in the best position to allow replacement of the missing tooth.

Examination of your mouth indicates that the risk of bone shrinkage is high and that your dentist needs to build up the bone foundation, to ensure that enough bone remains to allow implant treatment to be undertaken. The options available to the dentist include grafting of the extraction site immediately following removal of the tooth or grafting of the bone when the implant is placed in the mouth. Both treatment options are considered as standard treatment, with similar success rates recorded in each group.

What is the purpose of the research?

This research project is designed to measure changes to the shape and character of the bone and soft tissue following extraction of a tooth.

It tries to identify whether there is a difference in the character of the bone and soft tissues when grafting is undertaken immediately following removal of the tooth or when grafting occurs at the time of implant placement.

There are three different treatment groups under examination. They include bone grafting of the tooth extraction socket immediately after removal of the tooth, sealing of the extraction socket using a collagen membrane to encourage additional natural bone formation and no intervention, where normal bone and soft tissue healing occurs.

All three groups will be planned for implant placement at 4 months. Further bone grafting may be undertaken on this occasion, if required, to allow complete bone coverage of the implant and placement of the dental implant in the best position to allow replacement of the missing tooth.

All three groups will be treated using the same bone and collagen grafting material which is derived from cow and pig animal products. The grafting material has the ability to encourage bone and soft tissue formation, but it is the body's natural healing potential that is being measured.

The differences between the groups will be assessed by measurements recorded in the mouth, x-ray examination and bone samples collected when the implant is placed.

The research will examine whether immediate grafting of the extraction site, retains sufficient bone tissue to allow implant placement without the need for additional bone grafting. It will also examine whether there are differences in the appearance of the final restorations, the quality of the supporting tissue and the overall patient experience.

A copy of the timeline for the research is attached

Who is doing this research?

The assessment and treatment of your dental disease will be undertaken by Wg Cdr N Macbeth, the Consultant in Restorative Dentistry, at the Centre for Restorative Dentistry (CRD) in Aldershot.

Why have I been invited to take part?

Following the extraction of your tooth, shrinkage and remodelling of the surrounding tissue will occurs as a part of the normal healing process. In some people, the risk and the amount of remodelling that occurs is greater. This is normally because of past infection at the site or when very little bone is present surrounding the root of the tooth.

Several different successful treatment options have been developed to reduce the severity of the bone loss and make the implant treatment easier. The three best treatment pathways are examined in this research project. Without the use of one of these pathways, the dentist may not be able to place the implant, or the implant may have to be placed in an unfavourable position, affecting the appearance of the replacement tooth and the ability to clean around the restoration.

Do I have to take part?

No, you are under no obligation to take part in this study.

You will be able to receive the full range of implant and bone grafting treatment options offered within the CRD department, if you decline to be take part.

What will I be asked to do?

You will be asked to attend the dental clinic on 10 separate visits, over a 12-month period, to allow for assessment of your mouth, extraction of the tooth, grafting of the socket, placement of a dental implant and replacement of the missing tooth.

Involvement in the study will involve only one additional visit to the CRD department, with a summary of the timing and stages involved in the treatment provided in the attached flow chart.

What is the device or procedure that is being tested?

1.The ability of different surgical techniques to retain and preserve the soft tissue and bone at a tooth extraction site.

2. The requirement to graft the bone site, to allow the dentist to place the dental implant in the best position.

3. The rate of healing will also be measured, to determine whether any of the techniques is more effective at retaining the bone and soft tissue material over a longer period.

What are the benefits of taking part?

All three of the treatment options are considered as standard treatment associated with the successful replacement of a tooth using an implant supported restoration.

Initial preservation of the tissues or grafting of the bone site at implant placement helps to establish a healthy bone and soft tissue foundation, without the requirement to use complex grafting procedures. The grafting procedures increase the thickness of the bone layer to allow optimal implant placement, reduces the long-term risk of bone resorption and helps in the development of a stable and healthy implant to bone connection.

Retention of the soft tissues helps to ensure that the appearance of the false tooth is improved and that the risk of developing gum inflammation and bone loss around the implant crown is reduced.

What are the possible disadvantages and risks of taking part?

Although the treatment may require that a slightly more complex surgical procedure be adopted, when the tooth is extracted, it should not increase the likely hood of implant failure, infection or tissue shrinkage at the extraction site. If breakdown of a grafted site does occur, the healing process in the bone tissue should progress in an unaffected way, but the site may require further bone grafting when the implant is placed

It is important that you are aware that that all dental implants have a 2 -5% risk of early failure, due to the failure of the bone to heal around the implant. This may be associated with your medical history or another social factors (past smoking habits).

The provision of an implant-supported restoration also requires that a regular maintenance programme be established with your dentist, to ensure that the health of the gum and bone tissues are maintained around the implant. This treatment will be provided by the Defence Dental Service during your military career but cannot be routinely accessed through routine NHS dental services. Provisions should be made for this long-term maintenance cost before you leave the military.

Can I withdraw from the research and what will happen if I don't want to carry on?

Yes, you can withdraw from the research programme at any stage of the treatment.

On this occasion, your planned implant treatment will be completed as recommended by Defence Dental Service treatment guidelines.

If you don’t want to carry on with dental implant treatment, an explanation of the implications, risks and outcomes of the withdrawal will be discussed. Alternative treatment options will then be offered and provided to replace your missing tooth.

Are there any expenses and payments which I will get?

No, there are no payments or expenses provided for participation in this project.

Will my taking part or not taking part affect my Service career or medical care?

Participation in this study may affect you Service career as it will affect your ability to be deployed during the study.

No medical effect on your medical care should result from participation in this study.

Whom do I contact if I have any questions or a complaint?

If you have any questions or concerns relating to this study, you can contact Wg Cdr MacBeth directly within the CRD department. Alternatively, you can discuss any concerns with the practice manager Sgt Claire Danby. The contact point for any correspondence is MOD Tel: 94222 2895, BT: 01252 347895.

What happens if I suffer any harm?

All direct surgical treatment has a risk of physical tissue damage. This may present as pain, inflammation and swelling, with local tissue recession, remodelling and adjacent tooth sensitivity occurring. Although these inherent risks are anticipated as part of the interventional procedure, they will not be considered as adverse risk event in the context of this study.

Individuals, who sustain an injury or illness as direct result of this study, may submit a claim to The Ministry of Defence, who run a no-fault compensation arrangement for personnel who volunteer to participate in a Trial approved by the MoD Research Ethics Committee.

What will happen to any samples I give?

All study documentation (forms, investigators files, patient radiographs and photographs) will be kept at the CRD department after the study is completed for at least 11 years and the Investigator(s) should be available during this time to answer any queries associated with the study. These records will then be archived according to Defence Primary Health Care and MOD archive procedures.

Histology samples will be sent to an external lab for analysis, but all patient details will be anonymised, with the samples returned to the CRD department upon completion of treatment.

Will my records be kept confidential?

All clinical records specific to the clinical study will be anonymised and stored in the CRD department. Initial consultation records, letters of correspondence and digital X-rays will be added to your normal electronic medical recorded as detailed by the Defence Dental Service policy documents.

Originals of the study clinical data forms, casts or other items and originals of the study records shall be stored in a secured location within the CRD department. A digital back up of recorded digital x-ray images will be saved on an external hard drive and positioned in a fire-poof safe at the end of every session. You will be provided with a letter with full disclosure of the medical devices utilised during your care at the completion of treatment.

Who is organising and funding the research?

This study has been sponsored by the Surgeon Generals Research Strategy Group for the costs of the programme and the histological analysis of the alveolar bone samples.

The Defence Dental Service has agreed to provide funding for the clinical and surgical components of this study.

The analysis of the alveolar and gingival tissue grafting procedures using the CAD / CAM Nobel Procera system has been supported by the American division of the Nobel-Biocare implant company.

Who has reviewed the study?

This study has been reviewed and given favourable opinion by the Ministry of Defence Research Ethics Committee (MoDREC).

Further information and contact details.

Wg Cdr Neil MacBeth CRD Department, DDS Aldershot, Evelyn Woods Road, Aldershot. Tel: 94222 2895, BT: 01252 347895)

Compliance with the Declaration of Helsinki.

This study complies, and at all times will comply, with the Declaration of Helsinki[2] as adopted at the 64th WMA General Assembly at Fortaleza, Brazil in October 2013.

[2] World Medical Association Declaration of Helsinki [revised October 2013]. Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects. 64th WMA General Assembly, Fortaleza (Brazil).

Appendix D

Adverse Event Log

Centre For Restorative Dentistry

DPHC (Dental)

Wg Cdr N MacBeth

MODREC NDM 653

Adverse Event Log - Visit Type / Number

AE Number	Adverse Event	Duration			Severity (1 / 2 / 3)	Study Categorization 1. Implant 2. Graft 3. Tissue 4. Other Tick the relevant category and complete further AE category information				Relationship to study category	Action taken	Outcome 1= resolved 2 = persisting 3 = death 4 = unknown	Reported as serious Yes / No
		Start date	Stop date	Tick if Ongoing									
1		__/__/__	__/__/__			1	2	3	4				
2		__/__/__	__/__/__			1	2	3	4				
3		__/__/__	__/__/__			1	2	3	4				
4		__/__/__	__/__/__			1	2	3	4				
5		__/__/__	__/__/__			1	2	3	4				
6		__/__/__	__/__/__			1	2	3	4				
7		__/__/__	__/__/__			1	2	3	4				
8		__/__/__	__/__/__			1	2	3	4				

SEVERITY: 1=MILD 2=MODERAT 3=SEVERE
OUTCOME: 1=RESOLVED 2=PERSISTING 3=DEATH 4=UNKNOWN
RELATIONSHIP TO STUDY 1=NOT RELATED 2=DOUTFUL 3=POSSIBLE 4=PROBABLY 5=VERY LIKELY
ACTION TAKEN: 1=NONE 2=STUDY STOPPED 3=OTHER (SPECIFY)

Type of SAE

Results in Death ☐
Life threatening ☐
Hospitalisation or prolongation of hospitalisation ☐
Persistent or significant disability or incapacity ☐
Congenital anomaly or birth defect ☐
"Other" important medical event ☐
If "Other", please describe:
……..

CHIEF/PRINCIPAL INVESTIGATOR

SIGNATURE: _____ DATE: _____ / _____ / ___

Concomitant Medications Log

Medication	Dose	unit	frequency	Duration			Indication (e.g. Associated Illness, Implant, graft, tissue)	Specify route if different from oral
				Start date	End date	Tick if ongoing		
				__/__/__	__/___/__			
				___/___/___	___/___/___			
				___/___/___	___/___/___			
				___/___/___	___/___/___			
				___/___/___	___/___/___			
				___/___/___	___/___/___			
				___/___/___	___/___/___			
				___/___/___	___/___/___			
				___/___/___	___/___/___			

CHIEF / PRINCIPAL INVESTIGATOR

SIGNATURE: _____ **DATE:** _____ **/** _____ **/** _____

ADVERSE EVENT CATEGORY (RELATED TO OTHER)

Description of the related event/Diagnosis:
(e.g., Intercurrent illness, cancer or malignant)

Visit type and number _____ and relevant AE no. _____

ADVERSE EVENT CATEGORY (RELATED TO IMPLANT)

Description of event/diagnosis:

Visit type and number _____ and relevant AE no. _____

Is the event related to?

Breakage/ Fracture of a drill tips or implant:	☐ Yes	☐ No
Displacement of a dental implant: (Sinus or nerve canal)	☐ Yes	☐ No
Displacement of augmentation material:	☐ Yes	☐ No
Perforation of the maxillary sinus:	☐ Yes	☐ No
Infection in the grafted area:	☐ Yes	☐ No
Infection around the implant:	☐ Yes	☐ No
No primary stability of dental implant:	☐ Yes	☐ No
Chronic pain:	☐ Yes	☐ No
Oro-antral fistula formation:	☐ Yes	☐ No
Loss of osseointegration of the implant:	☐ Yes	☐ No
Prosthesis failure: (Abutment or crown fracture)	☐ Yes	☐ No

ADVERSE EVENT CATEGORY (RELATED TO GRAFT ASSOCIATED EVENTS)

Description of event/Diagnosis:

Visit type and number _____ and relevant AE no. _____

Is the event related to?

Persistent pain in the grafted area:	☐ Yes	☐ No
Suppuration or expulsion of grafted material:	☐ Yes	☐ No
Tissue reaction to graft material:	☐ Yes	☐ No
Long term resorption and remodelling of the graft material:	☐ Yes	☐ No
Colour and tissue morphological changes:	☐ Yes	☐ No
Scarring and clefting of the gingival tissue:	☐ Yes	☐ No
Recession of the gingival tissue at the graft site:	☐ Yes	☐ No
Sensitivity from the adjacent dentition, due to root exposure:	☐ Yes	☐ No

ADVERSE EVENT CATEGORY (RELATED TO TISSUE COMPLICATIONS)

Description of event/Diagnosis:

Visit type and number _____ and relevant AE no. _____

Is the event related to?

Bone fracture	☐ Yes	☐ No
Osteomyelitis	☐ Yes	☐ No
Loss of osseointegration	☐ Yes	☐ No
Damage to adjacent or opposing dentition	☐ Yes	☐ No
Chronic pain	☐ Yes	☐ No
Local or systemic infection	☐ Yes	☐ No
Fistulas	☐ Yes	☐ No
Tissue recession	☐ Yes	☐ No
Dehiscence of soft tissue	☐ Yes	☐ No
Sequestration of graft material	☐ Yes	☐ No

Patient Screening number:	
Patient Randomization number:	
Patient initials:	
Date of birth:	
Gender:	

SAE in medical terms (diagnosis if possible):

Onset of first sign/ Symptom of SAE:

Day Month Year

AE code no:

Event description (including dates of hospitalisation)
If necessary, continue event description in Supplementary information section.

Why was the event considered serious?

Outcome at the time of report:

Did it result in a Serious Adverse Event (SAE):

Please tick the applicable

☐ Fatal

☐ Life-threatening

☐ Hospitalisation or prolongation of hospitalisation

☐ Results in persistent or significant disability/ incapacity

☐ Constitutes a congenital anomaly or a birth defect

☐ Other important medical event

If "Other", please describe: ……..

If one of the above is ticked, please report as SAE

Additional Outcome information

☐ Requires intervention to prevent one of the above outcomes

☐ Completely recovered

☐ Recovered with sequelae Day Month Year

☐ Condition improving

☐ Condition still present and unchanged

☐ Condition deteriorated

☐ Death Date of death: Day Month Year

Trial Device and associated components information

Type of Device	Brand name and model	Manufacturer	Implant Date	Explant date, if done	Causal relationship to SAE 1= No 2= Unlikely 3= Possible 4= Probable 5= Definite

Concomitant Medications and Medical History
Concomitant drugs relevant to the SAE

Trade Name	Indication	Total daily dose	Route of administration	Start date: Day Month Year	End Date: Day Month Year
					☐ tick if continuing
					☐ tick if continuing
					☐ tick if continuing
					☐ tick if continuing
					☐ tick if continuing

Patient's past medical history (e.g., Co-existing medical conditions such as diseases, allergies, similar experiences)

Date Day Month Year	Disease/ Surgery

Treatment of Event
Please describe treatment of event, including actions taken, medications given and relevant laboratory/ diagnostic test:

Additional/ Supplementary Information (Please indicate the section to which supplementary information refers)

I confirm that I have carefully examined all entries on the Case Report Form for this patient. All information entered by my colleagues or by myself is, to the best of my knowledge, correct as of the date below.

Signature Investigator: _____ **Date:** Day Month Year

Chapter 14

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