The Extent of Root Resorption Following the Application of Ascending and Descending Magnetic Forces: A micro-CT Study

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A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Clinical Dentistry (Orthodontics)

October 2011

Dedication

For my family and Ray.

Declaration

<u>Candidate Certificate</u>

This is to certify that the candidate carried out the work in this thesis in the Department of Orthodontics, University of Sydney and it has not been submitted to any other University or Institution for a higher degree

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Tiffany Teen Yu Huang

Acknowledgements

Special thanks to the following people:

Professor M. Ali Darendeliler for this opportunity to learn.

Professor Tamer Turk for his organization of the experimental step of this work.

Dr Carmen Gonzales and Dr Oyku Dalci for their guidance and assistance.

Dr Ersan Karadeniz for his help in tooth movement measurement and friendship.

Dr Angie Phelan for her help in magnet measurement and friendship throughout the course.

Associate Professor Allan Jones and Mr Dennis Dwarte for their help with the micro - CT and VG Studio Max software.

Associate Professor Peter Petocz for his help in statistical analysis.

My gratefulness to my family:

my parents Melissa and Eric, and

my brothers Raymond and Phil

for their unconditional love and support.

My true appreciation to my partner Ray who stood by me every step of the way.

My gratitude to those who have inspired, guided and supported me throughout this journey.

Contents

Abbreviations

ANOVA	Analysis of variance
BSP	Bonesialoprotein
cAMP	Cyclic adenosine monophosphate
CGRP	Calcitonin gene-related peptide
cN	centi-Newton
COX	Cyclooxygenase
CSF-1	Colony stimulating factor 1
DHCC	Dehydroxycholecalciferol
EARR	External apical root resorption
ECM	Extra cellular matrix
ECRM	Epithelial cell rests of Malassez
EGF	Epidermal growth factor
F	Fluoride
FE	Finite element
FEM	Finite element model
GAG	Glycosaminoglycan
HERS	Hertwig's epithelial root sheath
HF	Hydrogen fluoride
IGFs	Insulin-like growth factors
IL-1	Interleukin 1
IL-1β	Interleukin 1 beta

IL-6	Interleukin 6
IL-8	Interleukin 8
kV	Kilo volts
LIPUS	Low-intensity pulsed ultrasound
MFP	Sodium monofluorophosphate
Micro‐CT	Micro computed tomography
NaF	Sodium fluoride
Ni-Ti	Nickel Titanium
NSAID	Non-streroidal anti-inflammatory drugs
OIIRR	Orthodontically induced inflammatory root resorption
OPG	Osteoprotegrin
OPN	Osteopontin
OTM	Orthodontic tooth movement
PDL	Periodontal ligament
PGs	Prostaglandins
PGE1	Prostaglandin E1
PGE2	Prostaglandin E2
PTH	Parathyroid hormone
PTHrP	Parathyroid related protein
RANK	Receptor-activator of nuclear factor-Kappa
RANKL	Receptor-activator of nuclear factor-Kappa ligand
RR	Root resorption
SEM	Scanning electron microscopy
TGF-β	Transforming growth factor beta
TIFF	Tagged Image File Format

TNF-α	Tumor necrosis factor alpha
TNSALP	Tissue non specific alkaline phosphatise
TRAP	Tartrate resistant acid phosphatase
T/P	Tissue/ plasma rate
VIP	Vasoactive intestinal polypeptide
2D	Two dimensional
3D	Three dimensional
% wt	Dry weight percentage

1. INTRODUCTION

Orthodontically induced inflammatory root resorption (OIIRR) is an unavoidable side effect of orthodontic treatment. Orthodontic force activation creates compression and tension zones in the PDL with hyalinization occurring in over compressed zones. Root resorption (RR) occurs from the loss of mineralised cementum and dentine concurrent with removal of hyalinized tissue [1-3].

The aetiology of OIIRR is multifactorial with risk factors classified under three main groups: biological, dental and mechanical risk factors. Biological factors include genetic factors[4-6], ethnicity[7], endocrine imbalances[8-11], nutrition[8,9,12], asthma and allergy[13-15], gender[4,7,16,17], chronological and dental age[4,12,18,19], medications[20-23] and habits[17,24-26]. Dental risk factors include root shape and dental anomalies[27-31], history of trauma[12,24,32,33], endodontically treated teeth[34-37], presence of RR before orthodontic treatment[19], periodontal status[38-40], proximity of cortical plate[41], alveolar bone density and turnover rate[42-44]. Mechanical risk factors including the treatment duration[30,45-50], type of appliance[12,51-54], magnitude of applied force[55-61], duration of force application[62-66], type and extent of tooth movement[67-69], and extraction and non extraction treatment[51,68,70]. There is still no consensus in the literature regarding most of these risk factors.

Magnetic forces have been used in orthodontics for tooth movement[71-75] with varying degrees of success. Using magnets, it is possible to deliver gradual and smooth change in force magnitude with the force produced by the magnets inversely proportional to the fourth root of the distance between them[76]. In addition, magnets deliver predictable force levels with no loss of force and provide frictionless mechanics[77,78]. Magnets are capable of delivering either ascending or descending force magnitudes by being positioned in attraction or repulsion orientations respectively.

Currently there is no reported human studies of OIIRR utilising ascending and descending forces using magnetic appliances. The aim of this study was, therefore, to investigate the amount of OIIRR and tooth movement using ascending and descending forces generated by magnets.

2. REVIEW OF THE LITERATURE

The process of tooth movement and RR consists of the complex interaction between alveolar bone, PDL and root cementum. The biology of periodontium is therefore vital in the understanding of the biology of tooth movement, RR and repair process.

2.1. Periodontium

The periodontium is comprised of alveolar bone, root cementum, periodontal ligament, and dentogingival junction[79].

2.1.1. Bone

Bone provides structural support for the body and serves as a reservoir for the maintenance and balance of mineral, acid-base, growth factors, cytokines and haematopoiesis within the marrow spaces[80]. It has a high dynamic capacity for remodelling. Bone minerals (calcium phosphate crystals and hydroxyapatite) provide mechanical rigidity and load-bearing strength to bone, whereas the organic matrix provides elasticity and flexibility. It consists of 50-70% mineralized matrix, 20-40% organic matrix, 5-10% water and <3% lipids[80].

2.1.1.1. The Structure of Bone

At macroscopic level, the adult human skeleton is composed of approximately 80% cortical bone and 20% trabecular bone overall[80,81]. Cortical bone is dense and solid and surrounds the marrow space[80]. It is typically less metabolically active than trabecular bone[80,81]. Trabecular bone is composed of a honeycomblike network of trabecular plates and rods interspersed in the bone marrow compartment[80]. It is less dense, more elastic and has a smaller Young's Modulus and a higher turnover rate than cortical bone[82].

At microscopic level, bone is consisted of two distinct types: woven bone and lamellar bone.

Woven bone has an irregular, disorganized pattern of collagen fibre orientation and osteocyte distribution. Rapid production of woven bone can be caused by mechanical stimulation. Woven bone is ultimately remodelled into dense, lamellar bone, indicating its responses to changes in functional activity[83,84].

Lamellar or mature bone is found in both cortical and trabecular bone. In cortical bone, the structural subunits, the lamellae, are arranged in osteons; whereas in trabeculae bone, the lamellae run parallel to it[82,83].

At ultrastructure level, three distinctly different cell types can be found within bone: the matrix-producing osteoblast, the tissue-resorbing osteoclast, and the osteocyte[83].

Osteoblasts are the cells that lay down the extracellular matrix and regulate its mineralization within the bone. They are cuboidal in shape and, together with their precursors, form a tight layer of cells at the bone surface[83]. Mature active osteoblasts secrete type I collagen and other matrix proteins vectorially toward the bone formation surface[80]. They also secrete cytokines, growth factors and bone morphogenetic proteins[85].

Some osteoblasts that become trapped in their own calcified matrix, change their phenotype and develop into osteocytes. Osteocytes are the principal cell in adult bone, and they can make and possibly also resorb bone[86].

Osteoclasts have ability to resorb fully mineralized bone at sites called Howship's lacunae[83]. They bind to bone matrix *via* integrin receptors in the osteoclast membrane linking to bone matrix peptides. Binding of osteoclasts to bone matrix causes them to become polarized, with the bone resorbing surface developing a ruffled border which secretes hydrogen ions[80,87]. Each osteoclast can resorb approximately $2x10^5$ μm^3 /day of bone tissue which is equivalent to the amount of bone produced by 7-10 osteoblasts.

2.1.1.2. Bone Biomechanics

2.1.1.2.1. Bone Formation - Osteogenesis

Bone formation is a process of osteoid formation by osteoblasts followed by hydroxyapatite precipitation[88]. There are two types of ossification: endrochondral and intramembraneous ossification.

In endochondral ossification, a precursor hyaline cartilage firstly forms the general shape of bone[89]. Mesenchymal cells migrate to the site of the future bone and differentiate into chondroblasts. Afterwards, the perichondrium turns into periosteum and cells in this region become osteoblasts. Osteoprogenitor cells from periosteum then migrate into the cavity with the blood vessels and cartilage model eventually is replaced by bone[89].

In intramembranous ossification, bone is formed by osteoblasts which are directly differentiated from mesenchymal cells[89]. Mesenchymal cells migrate to the intended bone formation site and then differentiate into osteoblast which secrete matrix collagen and other components of bone matrix. Eventually, the bone matrix calcifies and osteoblasts become osteocytes[89].

2.1.1.2.2. Bone Resorption

Bone resorption occurs as a result of osteoclasts removing the extracellular matrix of bone. Osteoclasts bind to bone matrix via integrin receptors on the osteoclast membrane linking to bone matrix peptides[80]. In active form, osteoclasts become polarized forming three distinct membrane domains: a ruffled border, a sealing zone and a functional secretory domain. Hydrochloric acid and proteases (cathepsin K) are delivered to an area between the ruffled border and the bone surface called the resorption lacuna (Howship Lacunae) whereby crystalline hydroxyapatite is dissolved by acid, and the organic matrix is degraded by a mixture of proteases[90].

2.1.1.2.3. Bone Modelling and Remodelling

Bone has a great adaptability to changing metabolic and structural requirements via mechanisms of modelling and remodelling.

In bone modelling, the bones change their overall shape in response to physiologic influences or mechanical forces. In response to stimulating factors, independent action of osteoblasts and osteoclasts remove or add bone to the appropriate surfaces; hence, bone formation and resorption are not tightly coupled[80].

In bone remodelling, osteoclastic bone resorption are followed by osteoblastic bone formation. It occurs in 5 steps: (1) osteoclast activation, (2) removal of old bone by osteoclast, (3) osteoblast precursors deposit a cement line, (4) new bone deposition, and (5) osteoblasts become bone lining cells[85]. These remodelling processes of deposition and removal of bone tissue accommodate the growth of a bone without losing its function or its relationship to neighbouring structures[85]. This co-ordination between bone formation and resorption is controlled by the interaction and balance between receptor-activator of nuclear factor-Kappa ligand

(RANKL), receptor-activator of nuclear factor-Kappa (RANK), osteoprotegrin (OPG)[80].

2.1.2. Periodontal Ligament

Periodontal ligament is a specialized connective tissue situated between the root cementum and the bony socket wall[79]. The principal function of the periodontal ligament is in supporting the tooth in its socket, acting as ‘shock absorber’ to the masticatory forces, as a sensory receptor for proprioception, and as a reservoir for tissue homeostasis, repair and regeneration[79].

Six different types of principal fibre bundles (composed of several individual collagen fibrils which are usually Type I, III and XII) are present in periodontal ligament: the alveolar crest group, the horizontal group, the oblique group, the apical group and the interradicular group[91]. Principal fibres are embedded into hard tissue on both alveolar bone lining and cementum side, called Sharpey fibres which are fully mineralized in primary cellular cementum and only partially mineralized at their periphery in cellular cementum and bone[91].

Periodontal ligament is very well vascularised and innervated with the main blood supply from superior and inferior alveolar arteries and additional inter-alveolar vessels perforate the ligament horizontally. Nerve fibres in the PDL are orientated in the direction from apical region to gingival margin.

The principal cells of the periodontal ligament are fibroblasts with numerous other cells including: epithelial cells, undifferantiated mesenchymal cells and bone and cementum cells. The fibroblasts are aligned through the direction of principal fibres, have an exceptionally high rate of protein turnover and also able to synthesize and degrade collagen[91].

A major constituent of the PDL, the ground substance, is an amorphous background material that binds tissue and fluid, facilitates the diffusion of metabolic substances and acts as a stress breaker under loads[91].

2.1.3. Cementum

Cementum plays a major role in OIIRR. It is a heterogeneous, mineralized and avascular connective tissue that covers the anatomic roots of the teeth, on to which principal collagen fibres, Sharpeys fibres, anchor to the root surface[91]. Cementum has other functions including: the maintenance of occlusal relationship (adaptation), repair of root defects after resorption or fracture, and protection of the pulp[92].

Cementum has similar physical properties with bone; however, it is avascular, not innervated and exhibits little or no remodelling[93].

2.1.3.1. Composition of Cementum

Cementum is the least mineralized among the calcified dental tissues. It is composed of approximately 50% inorganic material (hydroxyapatite) and the remaining of collagen and non-collagenous proteins and water.

2.1.3.1.1. Organic Matrix

The main organic component of cementum is Type I collagen (~90%), and the proportion of Type III collagen is approximately 5%[94]. The collagen plays an important structural and morphogenic role including scaffold for mineralisation.

The predominant non-collagenous proteins in cementum are bone sialoprotein and osteopontin. They participate in the mineralization process by binding tightly to collagenous matrices and hydroxyapatite[94]. Other non-collagenous proteins include: alkaline phosphatase, dentin matrix protein1, dentin sialoprotein, proteoglycans, proteolipids, fibronectin, osteonectin, osteocalcin, tenascin, and several growth factors.[91]

2.1.3.1.2. Inorganic Matrix – Mineral Component

The mineral component of cementum consists of hydroxyapatite ($Ca_2(PO_4)_6(OH)_2$) with small amounts of amorphous calcium phosphates. The crystallinity of the mineral component is lower and the size of crystals smaller in cementum than in the other hard tissues. As a result, cementum has a greater capacity for absorption of fluoride and other trace elements over time but also more readily decalcifies in the presence of acidic conditions[94]. Cementum contains up to 1% fluoride, 0.5-0.9% magnesium, 0.1-0.3% sulphur and trace amounts of zinc, copper, sodium[94,95]. The mineral composition of cementum varies between subjects, within the same subject and between the different cementum types. In addition, a decreasing gradient in the concentrations of Ca, P, and F from the cervical to the apical third of the root has been reported[95].

2.1.3.2. Classification of Cementum

Different types of cementum have been identified, they vary in their location, function, structure, rate of formation, chemical composition and degree of mineralisation. It can be classified according to the time of its development before or after eruption (primary or secondary cementum), presence or absence of cementocytes in its structure (cellular or acellular cementum) and the origin of collagenous fibres of the matrix (intrinsic due to secretion by cementoclasts, or extrinsic referring to incorporation of periodontal ligment fibres)[96]. Acellular cementum covers the root dentine from cementoenamel junction to apex but it is often missing in the apical third of the root; whilst cellular cementum is located mainly at the apical third portion of the tooth in humans[96].

Three fundamentally different human cementum which can vary from tooth to tooth or from region to region on the same tooth are described[94]: Acellular Afibrillar Cementum, Acellular Extrinsic Fibre Cementum, and Cellular Intrinsic Fibre Cementum.

2.1.3.2.1. Acellular Afibrillar Cementum

Acellular afibrillar cementum is deposited as isolated patches over minor areas of enamel and dentin at or just above the CEJ. It appears similar to the matrix of acellular extrinsic fibre cementum (see below), but contains neither collagen fibrils nor embedded cells, and therefore indicative of its lack of function in tooth attachment[94].

2.1.3.2.2. Acellular Extrinsic Fibre Cementum

The acellular extrinsic fibre cementum is usually confined to the cervical and middle thirds of the tooth. It can extend towards the apex on the anterior teeth. Its formation commences therefore shortly after crown formation is completed and always before cellular intrinsic fibre cementum starts to form on more apical root portions[94].

This cementum matrix has high density of collagenous fibres which are continuous with the matrix of the dentine. The extraordinarily high numerical density of fibres (Sharpey's fibres) inserting into acellular extrinsic fibre cementum (approximately 30,000/mm^2) is a reflection of the significant function of this cementum type for tooth anchorage to the surrounding bone[94,97]. The calcification of this cementum is approximately 45-60% with less mineralized innermost layer and the outer layers characterized by alternating bands that run parallel to the root surface[91].

2.1.3.2.3. Cellular Intrinsic Fibre Cementum

Cellular intrinsic fibre cementum is distributed along the apical third or half of the root and in furcation areas where no acellular extrinsic fibre cementum has been deposited on dentine[79]. This type of cementum tends to be the type formed when repair of root resorption occurs due to its capacity to grow much faster than any other known cementum type[94]. This cementum type is less mineralized than acellular extrinsic fibre cementum due to its heterogeneous collagen organization, its rapid speed of formation, and the presence of cells and lacunae[79].

2.1.3.3. Development of Cementum

Root formation is guided by the formation of Hertwig's epithelial root sheath (HERS), which is a collar of epithelial cells resulting from the apical elongation of the enamel organ[91]. There are two different theories regarding initiation of cementum formation. Firstly, infiltrating dental follicle cells differentiate into cementoblasts after receiving a reciprocal inductive signal from dentin surrounding HERS. Secondly, HERS cells transform into cementoblasts. In both theories, the fragmented cells of the HERS form a discrete mass called epithelial cell rests of Malassez[91]. The disintegration of cervical HERS prior to cementogenesis to allow for the perforation and gradual penetration of HERS by mesenchymal cells constitutes a key point for the cementogenesis[98].

2.1.3.4. Distribution of Cementum

The thickness of cementum is approximately 50 μm in the cervical margin and around 200μm at the apex[91]. Acellular afibrillar cementum is limited to the cervical enamel region. From cervical margin extending at least two thirds of the root is acellular extrinsic fibre cementum. At the apical third and interradicular regions cellular cementum is located. In addition, a linear relationship exists between the thickness of the cementum and age, with the average thickness of cementum increasing from 0.1 to 0.2mm from the age of 20 to 55[99].

2.2. Tooth Movement

Orthodontic tooth movement can be defined as the result of a biological response to interference in the physiological equilibrium in the dentofacial complex by an externally applied force[100]. It is a process that involves both pathologic and physiologic responses to externally applied forces[101]. When prolonged pressure is applied to a tooth, the bone around the tooth and even sutures distant from the tooth remodels resulting in selective resorption and apposition of bone[100].

2.2.1. Theories of Tooth Movement

Two main theories for tooth movement have been proposed: the application of pressure and tension to PDL and the bending of the alveolar bone.

2.2.1.1. The Pressure-Tension Theory

Histological studies on tooth movement by Sandstedt[102], Oppenheim[103] and Schwarz[104] postulated that tooth moves in the periodontal space by generating a "pressure side" and a "tension side". On the pressure side, vascular constriction results in reduced cell replication and the PDL displays disorganisation and diminution of fibre production. On the tension side, stretching of the PDL fibre bundles results in increased cell replication and enhanced proliferative activity which leads to increased PDL fibre production[105].

Sandstedt was first to describe direct and indirect resorption[102]. With light forces the bone was resorbed directly by multinucleate osteoclasts in Howships lacunae (direct/frontal resorption). With heavy forces, there was capillary thrombosis, cell death and cell free zones (hyalinisation), whereby osteoclastic resorption of the adjacent alveolar wall occurs from neighbouring marrow spaces (indirect/undermining resorption). The removal of this hyalinised necrotic tissue starts when cellular elements such as macrophages, foreign body giant cells and osteoclasts from the adjacent undamaged areas invade the necrotic tissue. These cells resorb the underside of bone immediately adjacent to the necrotic PDL area and remove it together with necrotic tissue. This was described histologically by Reitan[106].

Schwarz[104] proposed that orthodontic force should not exceed the capillary bed blood pressure (20-25 g/cm^2 of root surface). If the pressure exceed this, compression would cause tissue necrosis through "suffocation of the strangulated periodontium"[104].

It was suggested that inflammation is at least partly responsible for cellular recruitment and tissue remodelling in the areas of force application. Bone remodelling in the periodontium consists of loss of bone mass at PDL pressure areas and apposition at tension areas[105,107].

2.2.1.2. The Bone Bending - Bioelectric Theory

Farrar[108] was the first to suggest that alveolar bone bending plays a major role in orthodontic tooth movement. This theory was supported by Baumrind[109] in rats which demonstrated the crown of the tooth was displaced on average 10 times more than the width of the PDL on the pressure side. It was also supported by human study by Grimm which showed interseptal bone deformations adjacent to tooth extraction sites[110]. According to this theory, when orthodontic forces are delivered to the tooth, they are transmitted to all tissues near force application, and these forces bend bone, tooth and solid structures of the PDL. Following bone bending, active biologic process involving bone turnover and renewal of cellular and inorganic fractions are accelerated while the bone is held in the deformed position[105].

However, bone bending theory contradicts the current orthopaedic dogma, which states that "any mechanical compression stimulates bone formation and tension stimulates bone resorption"[111]. This confusion was clarified by Epker and Frost by describing the change in shape of the alveolar bone circumference resulting from stretching PDL fibres[112]. The fibre stretching decreases the radius of the alveolar wall, that is, bending bone in the tension zone where bone apposition takes place. This is called the regional acceleratory phenomenon.

It has been proposed by Davidovitch et al.[113,114] that a physical relationship exists between mechanical and electrical perturbation of bone. They found electric currents enhanced cellular enzyme phosphorylation in PD tissues. Bone bending causes two types of stress-generated electrical effects (piezoelectricity and streaming potentials) which might function as pivotal cellular first messengers. Piezoelectricity is a phenomenon observed in many crystalline materials, in which a deformation of crystal structure produces a flow of electric current as electrons are displaced from one part of the lattice to another. However, two properties of piezoelectricity which do not correlate well with OTM: it has a quick decay rate (electric current is quickly produced and diminished even though the force is maintained) and it produces equivalent signal in the opposite direction upon force removal. The stress-generated potentials (streaming potentials) are small voltages produced when the ions in bone interact with the electric field when bone bends, producing temperature changes, i.e. a convection current. These potentials might affect the charge of cell membranes and macromolecules in the neighbourhood. Borgens[115] observed the generation of endogenous ionic currents evoked in intact and damaged mouse bones and suggested that the mechanically stressed bone cells themselves, not the matrix, are the source of the electric current.

Based on the above theory of OTM, Mostafa[107] et al proposed an integrated hypothetical model for tooth movement. This model consists of two pathways that work concurrently to induce tooth movement. Pathway I represents the more physiologic response as it is associated with normal bone growth and remodelling.

Whereas pathway II represents the generation of a local inflammatory response by orthodontic forces.

2.2.2. Phases of Tooth movement

Traditionally, tooth movement following application of orthodontic forces is divided into 3 phases by time as suggested by Burstone[116] (initial phase, lag phase and post lag phase) and Roberts[117] (initial strain, lag phase, and progressive tooth movement). The initial strain occurs in the first week as a result of PDL displacement (strain), bone strain and extrusion. This is followed by a lag phase which is characterized by low rate of tooth movement due to the hyalinization in compressed areas of the PDL. This phase coincides with the time it takes for cells within the marrow to differentiate and for the bone adjacent to the hyalinized tissue to be eliminated by undermining resorption. After completion of necrotic tissues removal, the progressive tooth movement phase starts. In this phase, the PDL is considerably widened and the osteoclasts is able to attack the bone surface over a much wider area. Provided the force is maintained light, bone resorption is predominantly of the direct type. This phase is characterized by gradual or sudden increases in tooth movement.

Recent studies[118,119] have suggested that tooth movement occurs in 4 phases. Phase 1 is the initial tooth movement due to the compression of the PDL. Phase 2 is characterized by the arrest of tooth movement as a result of hyalinization in the periodontal ligament. During phase 3, an accelerated continuous tooth movement occurs and continues until the biologic limit is reached. In Phase 4, tooth movement appears to be constant.

The biologic limit shows a great individual variability due to metabolic and genetic differences. Therefore, the duration of each phase and the maximum speed of tooth movement varies among the individuals.

2.2.3. Factors Affecting Tooth Movement

The purpose of orthodontic treatment is to move teeth as efficiently as possible with minimal adverse effects for the teeth and supporting tissue. Many factors affect the process of orthodontic tooth movement.

2.2.3.1. Force Magnitude

The relationship between force magnitude delivered by orthodontic appliances and the rate of orthodontic tooth movement remains controversial, as some proponents believe that different force levels produce the same amount and rate of tooth movement.

Quinn and Yoshikawa[120] proposed 4 hypothesis to explain the relationship between stress magnitude and the rate of tooth movement. (Figure 1)

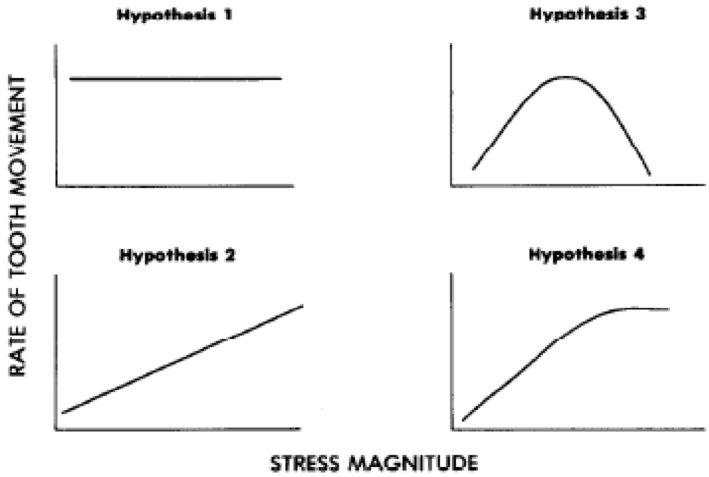

Figure 1. 4 Different tooth movement models suggested by Quinn and Yoshikawa[120]

Hypothesis 1 shows constant rate between force magnitude and the rate of tooth movement. According to this hypothesis there is a force threshold for tooth movement. Above this threshold, tooth movement will lead to the same rate of tooth movement. Owman-Moll[121] found that there was no significant difference when the force magnitude was doubled from 50cN to 100 cN. Iwasaki et al.[122] also found that when low magnitude continuous forces were applied on a tooth, the tooth movement does not show the lag phase.

Hypothesis 2 shows a linear increase in the rate of tooth movement above a force threshold. This hypothesis supports that higher forces are efficient in tooth movement. Hixon et al.[123] found a plateau at 300gm, which suggests this hypothesis may not be valid.

Hypothesis 3 was first proposed by Storey and Smith[124]. It shows increasing stress causes the rate of tooth movement to increase to a maximum. Once this optimal level is reached additional increase in force magnitude causes the rate of tooth movement to decline[120]. This hypothesis supports Begg's differential force concept[125] with high forces used as anchorage and low forces for space closure. These phenomena might be related to the induction of hyalinization in the periodontal ligament.

Hypothesis 4 shows the relationship between the rate of tooth movement and force magnitude is linear up to a point; after that, an increase in stress causes no appreciable increase in tooth movement. Boester and Johnston[126] also provided evidence that beyond certain level of stress, the rate of tooth movement no longer alters.

Von Bohl [127] stated that present models that describe the relationships between force magnitude and rate of tooth movement probably are not valid due to the many factors involved in tooth movement that are yet to be further investigated. For example, focal hyalinization probably does not directly depend on the applied force but on local stresses or strains that are individually and locally determined due to irregularities in periodontal and bone morphology[127].

Ren et al.[128] concluded that no threshold can be defined for the force or, more accurately, the increase in pressure that will switch on tooth movement, nor can an optimal force or force range be calculated that produces maximum tooth movement.

Proffit[100] recommended the optimum orthodontic force magnitudes for specific type of tooth movement in Figure 2.

Type of movement	*Force* (gm)*
Tipping	35-60
Bodily movement (translation)	70-120
Root uprighting	50-100
Rotation	35-60
Extrusion	35-60
Intrusion	10-20

*Values depend in part on the size of the tooth; smaller values appropriate for incisors, higher values for multirooted posterior teeth.

Figure 2. Optimum forces for orthodontic tooth movement by Proffit[100]

2.2.3.2. Types of Tooth Movement

In tipping movement, a fulcrum is created and the root moves toward the opposite site of the force. Tipping of a tooth with light forces produces greatest tooth movement than any other type of tooth movement. It causes a compression in limited areas of the PDL with maximum pressure created under the alveolar crest and at the root apex (Figure 3). Fulcrum and areas around the fulcrum are the least loaded. Therefore the orthodontic forces should be kept low for tipping movement[129].

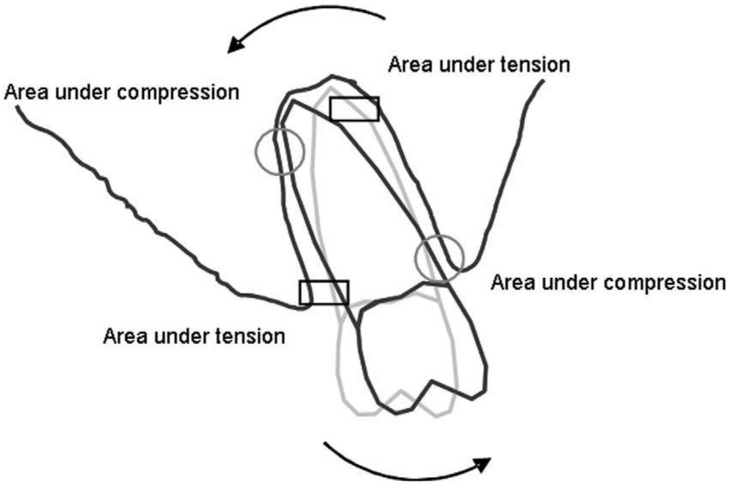

Figure 3. Diagrammatic representation of areas under compression or tension in buccal tipping[57]

Torquing movement involves tipping movement of the root apex. The first compression zone occurs in the middle third of the root. After removal of this compression areas by resorption, second compression area occurs at the apical surface of the root[129].

Bodily movement is created by force couples which act in parallel lines and spread the force evenly over the alveolar bone. The forces used in this type of movement cannot exceed a certain level[129].

Rotation forces are distributed within entire PDL; therefore, larger forces can be applied than any other movements[129].

During extrusion, no compression zones are created within the PDL but tension[129].

During intrusion, force is usually localized in a small area at the root apex in intrusion, so force magnitude should be carefully selected[129].

2.2.3.3. Force Duration

Orthodontic tooth movement can only be created by sustained force application for a certain period of time. A least 4 hours is required to induce the cytokine effect. Increasingly effective tooth movement is produced if force is maintained for longer durations. There is a decline in force magnitude as tooth moves in response to that force. From this perspective orthodontic force duration is classified by the rate of decay as follows[100]:

Continuous force*:* Force maintained at some appreciable fraction of the original between the appointments[100]. Examples include Ni-Ti coil spring[130] and drum spring[131].

Interrupted force*:* Force levels decline to zero between activations. Examples include archwire, power chain and power thread[100].

Intermittent force: Force levels decline abruptly to zero intermittently, when a removable appliance is removed by the patient. Examples include removable appliances, head gear and elastics[100].

2.2.3.4. Growth and Age

The bone of children has a higher rate of remodelling than adults. The rate of orthodontic tooth movement in growing children is approximately twice that of adults[129]. A maximum rate of 2 mm per month for maxillary molar translation is possible with space closure mechanics or headgear in growing child, versus 1 mm per month in adults. Similarly, mesial translation of mandibular molars is approximately 0.7 mm per month in growing children versus 0.34 mm in adults[129].

In rats, Misawa et al.[132] found that the amount of tooth movement decreased with age. They suggested that the age-dependent decrease in alveolar bone turnover activity, in response to mechanical forces, may negatively affect the amount of tooth movement[132]. However, Ren et al.[133] showed in an animal study that although there was a faster initial tooth movement in juvenile than in adult rats, when tooth movement had reached the linear phase, the rate of tooth movement was the same in both groups.

2.2.3.5. Periodontal Health

After force application, immediate tooth movement occurs due to displacement within PDL, bone strain and extrusion. In healthy periodontium this rate is approximately 0.5 mm (0.3 mm periodontal displacement and 0.2 mm bone strain and extrusion). However, in unhealthy periodontium with alveolar bone loss, this movement can exceed over a millimetre. In periodontal disease, bone formation is suppressed and bone resorption is even enhanced; thus the tooth movement remodelling process results in rapid loss of supporting bone[129].

2.2.3.6. Bone Density

The rate of orthodontic tooth movement is inversely related to bone density. The density of alveolar bone in maxilla is less than the mandible because it has a higher ratio of cancellous to cortical bone. Cancellous bone has more surface area available for resorption and more osteoclasts present to remove the osseous tissue impeding tooth movement[129].

2.2.3.7. Metabolic Bone Disease

Orthodontics is usually contraindicated in patients with active metabolic bone disease, such as osteoporosis, due to excessive resorption and poor bone formation[134]. The risk factors for developing osteoporosis include age, long term glucocorticoid treatment, slight stature, smoking, menopause, low physical activity, low calcium diet, excessive alcohol consumption, vitamin D deficiency, kidney and liver failure and history of fractures.

2.2.3.8. Hormonal Influence

Hormones that have a major impact on orthodontic tooth movement include: sex hormones, relaxin, thyroid hormones, parathyroid hormone and Vitamin D[135].

Estrogen inhibits cytokine production and bone resorption and is the most important hormone related to bone metabolism in women[136]. Women taking oral contraceptives or taking estrogen supplement for menopause might experience slow tooth movement due to a reduced rate of bone metabolism[137].

Relaxin has been suggested as an adjunct to orthodontic therapy during or after orthodontic treatment for the promotion of stability by reducing the stretched soft tissue and rapid remodelling of gingival tissue[135].

Thyroxin increases bone remodelling and resorptive activity and reduces bone density. This is due to induced interleukin-1 production which appears to stimulate osteoclastic activity[138-140]. Therefore, patients taking thyroxin should have increased orthodontic tooth movement.

Parathyroid hormone (PTH) affects osteoclastic activity through the production of RANKL. It has been shown that PTH increases the rate of orthodontic tooth movement when applied either locally or systemically[141,142].

Vitamin D is synthesized in the skin irradiated by UV light and hydroxylated in liver and kidney to become 1,25 dehydroxycholecalciferol (DHCC)[129]. Intraligamentous injection of 1,25 DHCC demonstrated increases in the number of osteoclasts and the amount of tooth movement in cats[143].

2.2.3.9. Pharmacological Agents

The main categories of pharmacological agents that can influence orthodontic tooth movement include: eicosanoids, non steroidal anti inflammatory drugs, corticosteroids, calcium and calcium regulators and fluoride.

Eicosanoids are involved in several regulatory and pathologic processes including inflammatory and immune responses, vasodilation and vasoconstriction[144]. They are divided into four different families leukotrienes, thromboxanes, prostacyclins, and prostaglandins.

Leukotrienes play an important role in inflammation, allergies, and diseases such as asthma. Mohammed et al.[145] demonstrated the inhibitory effect of leukotriens on orthodontic tooth movement.

Prostaglandins play a major role in inflammation[144]. Local injection of PGE 1 and PGE2 has been shown to increase the rate of tooth movement in monkeys[146,147]. PGE2 was shown to have a dose dependent effect in rats[148] and that the reduced rate of PGE2 synthesis also decreased the rate of tooth movement in rats[149].

NSAIDS including aspirin, diclofenac, ibuprofen and indomethacin were shown to reduce orthodontic tooth movement. Yamasaki et al.[150] found that indomethacin which is a non steroidal COX 1 and COX 2 inhibitor reduced bone resorption and OTM in rats. However, Celecoxib was found to have no influence on orthodontic tooth movement.

Corticosteroids are used for many inflammatory and autoimmune diseases. In rats, corticosteroids reduced the rate of bone turnover in short term; however, in long term it increased rate of tooth movement[151].

Bisphosphonates inhibit osteoclastic activity and are used for the treatment of several metabolic bone diseases. In rats, local application of clodronate (a bisphosphonate) without the nitrogen atom reduces the amount of OTM and the number of osteoclasts[152].

The effect of fluoride on orthodontic tooth movement was investigated in animal studies. Fluoride reduced rate of orthodontic tooth movement and reduced osteoclasts on the pressure side of the PDL in rats[153]. Gonzales et al[154] found that, when administered from birth, fluoride reduced the amount of tooth movement and the duration of fluoride administration affected the amount of tooth movement in a time-dependent manner, i.e. the longer the fluoride was administered the smaller the amount of tooth movement.

2.2.3.10. Dietary Factors

The composition of diet may have important effects on tooth movement. A favourable diet is directly related to maintaining the calcium metabolism. In animal study on beagle dogs, a low calcium diet caused a state of hyperparathyroidism which lead to increased rate of bone turnover and tooth movement and reduced bone density with significant reduction of trabecular bone[155].

2.2.3.11. Electromagnetic Influences

The cellular reactions after application of orthodontic force maybe enhanced by an electromagnetic field of either static or pulsed types[156-158]. The application of a non-invasive, pulsed electromagnetic field increased the rate of orthodontic tooth movement and bone deposition in guinea pigs[158]. Also, greater amounts of bone and matrix were deposited in the tension area between orthodontically moved maxillary incisors as well as significantly greater numbers of osteoclasts in the surrounding alveolar bone[158]. Darendeliler et al.[159] investigated the effect of electromagnetic fields in combination with the use of coil spring. Their results showed that both the static magnetic field produced by the samarium-cobalt magnets and the pulsed electromagnetic field used in combination with the coil spring were successful in increasing the rate of tooth movement over that produced by the coil springs alone. The mechanism appears to involve a reduction in the lag phase[159].

2.3. Root Resorption

2.3.1. Definition of Root Resorption

Root resorption is a physiological or pathological process that involves the active removal of dentine and mineralized and non-mineralized cementum[160]. Physiological root resorption occurs during the exfoliation of the deciduous dentition. Pathological root resorption can be either internal or external in origin. In internal root resorption, the process is originated from the cells in the pulp and affects the internal wall of dentin and pulp. Whereas external root resorption is initiated from periodontium and affects the external and lateral surfaces of the root.

2.3.2. Classification of Root Resorption

There are many different types of pathological RR and it has been classified by several authors[161,162].

Andreasen[161] classified external root resorption into three types:

1. Surface resorption which involves small surface areas of resorption and repair with new cementum by cells from the adjacent intact periodontal ligament. It is not usually detected radiographically.

2. Inflammatory resorption where the resorption has reached the dentinal structures of the necrotic pulpal tissues or an infected leukocytic zone. It is characterized by large resorption bays with inflammation and active root resorption.

   This type of resorption was further classified by Tronstrad[163] into

   a. *Transient inflammatory resorption* which occurs when root damage is minimal and the stimulus for the resorptive process is of short duration. It is usually repaired by cementum-like tissue, and is generally not detectable radiographically.

   b. *Progressive inflammatory resorption* occurs when the resorptive stimulus is of a longer duration and is detectable radiographically. The aetiology for this type of root resorption could be mechanical stimulation, pressure or infection. Depending on the site of microbial stimulation and resorption, it can be internal resorption or cervical resorption.

3. Replacement resorption where bone replaces the resorbed root structure and eventually leads to ankylosis.

Brezniak and Wasserstein[164] classified OIIRR according to its severity, based on the depth of the crater:

1. Cemental or surface resorption with remodelling: resorption involves only outer layer of cementum which will be fully regenerated or remodelled. This process has been compared to trabecular bone remodelling.
2. Dentinal resorption with repair (deep resorption): resorption process reaching cementum and outer layers of dentin and usually repaired with cementum material. The repaired contour of the root may or may not be distinguishable to the previous form.
3. Circumferential apical root resorption: all hard tissue components of apex are resorbed and root shortening results. Different degrees of root shortening are evident. When root structure is lost into dentine, no regeneration is possible.

2.3.3. Orthodontically Induced Inflammatory Root Resorption (OIIRR)

Root 'adsorption' in permanent teeth was first described by Bates[165] in 1856. In 1932 Becks and Marshal[166] stated that the term "resorption" is terminologically more appropriate. Ottolengui[167] was the first person to report apical root resorption related to orthodontic treatment. Later, Ketcham[168,169] showed this phenomenon in radiographs. Since then RR has been recognized as the side effect of orthodontic treatment and substantial amount of research has investigated the process of RR.

Orthodontic force application causes a biological process that shows five signs of inflammation which are redness, heat, swelling, pain and loss of function. Therefore, Brezniak and Wasserstein[164] proposed that orthodontic force induced root resorption should be termed "Orthodontically induced inflammatory root resorption" (OIIRR). OIIRR is an unavoidable pathologic consequence of orthodontic treatment. After the application of orthodontic force on a tooth, compression and tension zones in PDL are created. Root resorption occurs during the remodelling of the PDL to remove this hyalinised necrotic tissue in over-compressed regions[160].

2.3.3.1. Incidence of OIIRR

Many of the previous studies that examined the incidence of OIIRR utilised plain radiographs to identify the amount of root structure lost. Issues with radiographs include lack of standardisation and that it is a 2D technique which has limitations in assessing a 3D structure, i.e. resorption craters on buccal or lingual surfaces of root would not be visible on radiograph. Histological method has the limitation of information lost in between the thin sections examined.

Root resorption has been reported in both orthodontically treated and untreated individuals. Among untreated population, the prevalence ranges between 0-100%. Using radiographs, Ketcham[168] identified 1% of non-orthodontically treated patients showing signs of RR. Whereas, radiographic study by Massler et al.[19] found that 100% of the sample exhibited some evidence of periapical resorption in one or more permanent teeth. Histological study by Henry and Weinmann[170] on permanent human teeth from 261 orthodontically untreated people, reported 90% of untreated population exhibit root resorption. Most resorption occurred at the root apex, and there is an increase in resorption with increasing age[170]. Vlaskalic suggested that certain amount of root resorption is a normal physiological process and may occur during continuous hard tissue remodelling and turnover and transmission of occlusal forces through the dentition to the alveolar bone[50,171].

In orthodontically treated population, Lupi et al.[172] showed that the increased incidence of root resorption in adults from 15% before treatment to 73% after treatment. Moreover, moderate to severe apical root resorption in incisors increased from 2% before treatment to 24.5% after treatment. They also noted that the alveolar bone loss more than 1.5mm occurred in 11% of the incisors and 3% of the posterior teeth. Levander and Malmgren[30] reported severe root resorption increased from 1% before treatment to 17% after treatment and also 1% experienced an extreme resorption after 6-9 months of orthodontic treatment. Sameshima and Sinclair[173] examined pre and post-treatment periapical radiographs collected from 868 patients. They found less than 3% of the total patients (25 patients) had more than 20% root resorption on all four maxillary incisors. Linge and Linge[24] investigated the radiographs of 485 patients between 11.5 and 25 years of age and found that 16.5% of orthodontically treated patients had root shortening of more than 2.5 mm in one or more incisors.

The range and variety of the study findings is partly attributed to the limitation of 2D radiograph in assessing 3D RR, the variations in sample groups and sizes. These studies cannot be directly compared; however, they showed a general trend of most teeth exhibit some degree of RR without orthodontic treatment, and the RR increases with treatment.

2.3.3.2. Diagnosis of OIIRR

Radiographs are most commonly used to clinically diagnose OIIRR. Dental panoramic tomography (OPG) provides an overall view of the dentition with lower radiation dose than a full-mouth series of intra-oral radiographs[174]. Radiography is one of the 2D techniques used in assessing RR; other 2D methods include light microscopy and scanning electron microscopy (SEM). All these methods reflect a three dimensional object into a two dimensional image. Even though quantitative analysis can be performed using 2D methods, these images do not represent the actual morphology of the object.

Radiographic technique was shown to not able to detect medium to large size resorption cavities on the buccal and lingual surfaces of the root[175]. In addition, root resorption lacunae that reached half way to the pulp or more might not be detected by radiographs. Harris and colleagues[176] indicated that magnification errors in radiographs might lead to underestimation or overestimation of the amount of root resorption. Also, Sameshima and Asgarifar[177] reported that the use of panoramic films to measure pre- and posttreatment root resorption may overestimate the amount of root loss by 20% or more compared to periapical radiograph.

Light microscopy can be used in detection of craters; however, it cannot provide accurate quantitative analysis of resorption craters. Owman-Moll[121,178,179] introduced the method of histological sectioning combined with light microscopy; however, there was difficulty in detecting some small to medium sized craters especially in middle and apical third of the root.

SEM is used for both 2D and 3D evaluation of root resorption. In 2D, it can provide high resolution enhanced visual assessment of root resorption craters on the root surface.

3D evaluation methods of root resorption includes stereo-imaging-scanning, electron microscopy and computed tomography. SEM with stereo imaging can explore the third dimension of the resorption craters and has very high reproducibility and accuracy rates[180].

Currently, the best method to diagnose and quantify root resorption is computed tomography which has significant advantage over conventional radiography[181]. However, due to the high radiation exposure to patients, it is not routinely used clinically. Employing micro-CT on extracted teeth, RR can be assessed quantitatively and qualitatively with high sensitivity and accuracy.

2.3.3.3. Mechanisms of Root resorption

Following application of orthodontic force, the PDL becomes compressed, leading to areas of local inflammation and aseptic necrosis. This necrotic hyalinised zone is the key event that starts the chain reaction leading to root resorption. Elimination of this hyalinised tissue is carried out by an invasion of cells and blood vessels from adjacent undamaged periodontium. This results in alveolar bone resorption, allowing tooth movement to occur, but also leads to removal of cementum. The cellular mechanism involved in the resorption process is thoroughly investigated by Brudvik and Rygh[160,182-184].

This process continues until the hyalinised tissue is removed and the PDL is re-established. The duration of this process is dependent on the force magnitude and also force duration. Rygh claimed that elimination of the hyalinised tissue was completed after 20-25 days[185]. However, other studies indicate the resorptive process to continue up to a year[186-188].

The first cells that appear at the perimeter of hyalinised tissue are Tartrate-Resistant Acid Phosphatase (TRAP) negative cells[182]. These mononuclear TRAP negative cells remove the necrotic tissue at the periphery of the hyalinised zone, as well as the surface layers of unmineralised cementum and mineralised acellular cementum by phagocytic and collagenolytic activity[183]. The second stage involves mono- and multinucleated TRAP positive cells removing central part of the of the hyalinised zone, and continued resorption of the damaged and undamaged mineralised cementum[184].

Brudvik and Rygh also noted that the state of unmineralized cementum and its relationship with PDL is of importance for the development of OIIRR[183]. The normal cementum, PDL and cells covering the root surface contain a potent collagenase inhibitor which protects the root surface against resorption and if clastic cells breach this barrier and gain access to the root surface, resorption occurs[189]. The cementoblast layer might become damaged during the process of hyalinized zone removal; therefore, exposing the highly mineralized underlying tissue to resorptive cells[163]. It is also possible that orthodontic force application and overcompression can damage the surface layers of cementum[164].

After orthodontic force application, it takes 10-35 days for a resorption lacuna to appear, although they are usually too small to be detected radiographically[42,64,190]. After force application is ceased, root resorption by TRAP positive cells continued until the total elimination of existing hyalinized necrotic tissue is completed[189,191,192].

Recent studies have shown that osteoprotegerin (OPG), receptor activator of nuclear factor kappa B (RANK) and RANK ligand (RANKL) proteins are involved in the molecular processes of both physiological and orthodontic root resorption[193]. RANK is activated by binding either soluble or membrane-bound RANKL. RANK activation results in osteoclastic differentiation and activation and this interaction is blocked by OPG[194,195]. During orthodontic tooth movement on the compressed side of the PDL, RANKL expression is induced while on the tensile side an increased OPG synthesis was found[193]. The ratio between RANKL and OPG is believed to be involved in the root resorption process during orthodontic tooth movement. It has been shown that a great increase of RANKL and a decrease of OPG occurs in cases of severe root resorption[193,196-198].

2.3.3.4. Aetiology

The aetiology of OIIRR is multifactorial. Risk factors can be broadly classified under three groups: biological and environmental factors, dental factors, and mechanical factors. Despite extensive research, controversy still exists in the literature on most of these risk factors.

2.3.3.4.1. Biological and Environmental Factors

These factors are directly related to the patient, and may or may not be influenced by the patient and maybe either genetic or environmental in origin.

2.3.3.4.1.1. Genetics, Ethnicity and Individual susceptibility

Root resorption can occur in some individuals without orthodontic treatment, this illustrates the variation in susceptibility to root resorption. Individual susceptibility is considered one of the major factors determining root resorption potential not only for orthodontic root resorption but also for physiological root resorption. Rygh[185] noted that the root resorption process seems to vary between different individuals and also between different times within the same person.

Moreover, individual hormonal disturbances, systemic disease and cellular metabolism may change the individual response to disease and trauma[185]. In fact, individual reactions and metabolic response was suggested to have more impact on RR than the increase in the magnitude of force application or the length of treatment.[121,179].

Harris et al.[4] investigated genetic influence on susceptibility for root resorption and found 70% heritability in RR. It was also suggested that siblings experience similar levels of root resorption. Ngan et al.[6] investigated the genetic contribution of root resorption between mono and dizygotic twins and their results indicate a genetic component of root resorption. Al-Qawasmi et al. found a 5.6 fold increased risk of >2mm RR in individuals homozygous for the IL-1β allele 1[5].

Abass et al.[199] indicated that genetic factors account for approximately 64% of the external apical root resorption variation in humans. He also showed a traceable and polygenetic component affecting EARR in mice.

Using inbred mice, Al-Qawasmi et al.[200] studied the genetic susceptibility to RR and found certain genetic strains are highly susceptible, whereas other strains are more resistant to RR.

The effect of ethnical background on root resorption was investigated by Sameshima and Sinclair[7] on a sample of 868 patients from six different practices and found that Asian patients experienced significantly less root resorption than Caucasians or Hispanic patients. However, they later reinstated that their sample was disproportionate and may have resulted in biased outcomes[173]. Similarly

Smale et al.;[201] in a multicenter study of 290 patients, did not detect any racial differences.

2.3.3.4.1.2. Endocrine Imbalance

The metabolism of mineralized tissues is mainly regulated by three hormones; 1,25-Dihydroxycholecalciferol, Parathyroid hormone (PTH) and Calcitonin. An imbalance of these hormones have been found to influence RR.

- 1,25-Dihydroxycholecalciferol is derived from hydroxylation of vitamin D by in the liver and kidneys. Its primary function is to increase the calcium resorption from the kidney.
- PTH is secreted by parathyroid gland and its main function is to induce calcium release from bone and increasing renal calcium reabsorption and phosphate excretion from kidneys.
- Calcitonin is secreted by the thyroid gland. It inhibits osteoclastic activity and bone resorption.

In addition to these hormones, parathyroid related protein (PTHrP), phosphate-regulating hormone, glucocorticoids, growth hormone, oestrogens and various growth factors are also involved in bone metabolism.

Therefore, altered endocrine imbalance conditions such as hyperparathyroidism[9], Paget disease[10], hypophosphataemia[11], hypothyroidism, hypopituitarism and hyperpituitarism[202] are linked to altered rate of tooth movement and the amount of root resorption.

2.3.3.4.1.3. Nutrition

Root resorption has been demonstrated in animals deprived of dietary calcium and Vitamin D[8]. Engstrom and co-workers[8] reported that the severity of root resorption was related to alveolar bone resorption. Their experiment on rats showed that a calcium and vitamin D deficient diet induced hypocalcemia, increased alkaline phosphatase activity and PTH and increased number of osteoclasts in the PDL. It produced greater and more rapid bone resorption and more severe RR.

However, other authors proposed that nutritional imbalance is not a major factor in root resorption during orthodontic treatment[9,12]. Goldie and King[9] compared lactating rats deprived of dietary calcium and phosphorous with control group of normal diet. The diet deficient group showed greater amount of tooth movement and bone loss; however, there was a reduction in the size of the root resorption craters.

2.3.3.4.1.4. Asthma and allergy

Davidovitch et al.[14] found the incidence of asthma, allergies and signs of psychological stress were significantly higher in patients who had experienced excessive root resorption. Similarly, Nishioka et al.[15] reported that the incidence of allergy, asthma and root morphology abnormality significantly higher in patients with excessive root resorption.

In assessing risk factors associated with orthodontic root resorption (i.e. root morphology, gingivitis, allergy, nail-biting, medication, etc.), Owman-Moll and Kurol[203] found that only those subjects with allergies showed an increased risk of root resorption[14].

Increased incidence of RR was reported in chronic asthmatics[13]. It was postulated that the inflammatory mediators produced in asthma, may enter the periodontal ligament and act synergistically to enhance root resorption and may explain the resorption seen in roots near the inflamed maxillary sinus[13]. McNab et al.[13] showed that asthmatics had significantly more external apical root resorption of posterior teeth after treatment compared with the healthy group. They also added that although the incidence of external apical root resorption was elevated in the asthma group, both asthmatics and healthy patients exhibited similar amounts of moderate and severe resorption.

2.3.3.4.1.5. Gender, chronological and dental age

The association between gender and the incidence of root resorption is controversial. Most of the studies reported no correlation between gender and the extent of OIIRR[4,7,16]. Newman found females are more susceptible, with ratio of 3.7:1 for females to males[17]. Baumrind et al.[18], on the other hand, found male adult patients (age>20) had a greater prevalence of OIIRR. However, Kjaer[28] showed the opposite association between sex and OIIRR among adolescents.

With increasing chronological age, changes to the dentoalveolas occur and the PDL becomes denser, avascular and aplastic, and the thickness of cementum increases[43]. Adults also have aplastic alveolar bone surface, slow fibrous tissue reaction and slower the turnover rate of collagen molecules than younger patients[43]. These changes are thought to be responsible for the increased rate of root resorption in adults. However, relationship between chronological age and root resorption remains controversial. Several investigations [4,18,19,204] showed that age is not a significant factor for OIIRR. Whereas other studies disagree due to lack of significance in the results[7,12,43].

Dental age and the stage of root formation and their relationship to OIIRR has been investigated. It has been postulated that teeth with open apices may be more resistant to apical root resorption[12]. However, this was disagreed by Henrix et al.[16] who demonstrated that teeth with incomplete root formation did not reach their "normal" tooth length. This study employed radiographic examination with inherent limitation that may affect the measurement results[50].

2.3.3.4.1.6. Habits

Habits such as finger-sucking habits persisting beyond the age of 7 years[24], nail biting[26] and lip or tongue dysfunction[17,24] have been reported as risk factors to increased root resorption. Also, long-term orthopaedic forces from tongue thrusting associated with anterior open bites may promote increased root resorption[25].

2.3.3.4.1.7. Medications

Corticosteroids are anti-inflammatory and immunosuppressive medications used in several chronic medical conditions including allergy, asthma, dermatitis and eczema. Research on the effect of corticosteroid on OIIRR remains controversial. This could be due to the different animal models studied, different dosages of corticosteroids and also different duration[23].

Verna et al.[23] investigated the effect of acute and chronic corticosteroid treatment on external root resorption in rats. They reported increased root resorption in the acute corticosteroid group compared to chronic and control groups. Different dosage levels also affect RR differently; dosage as low as 1mg/kg oral prednisolone in rats reduced root resorption[22] while dosage as high as 15 mg/kg cortisone acetate in rabbits increased both tooth movement and root resorption[21].

Non-steroidal anti-inflammatory drugs (NSAIDs) are common medications for treatment of pain, inflammation and fever. Research studies have reported different effect of NSAIDS: reduction of tooth movement[205,206], reduction of RR[20], and both[22].

Bisphosphonates are potent inhibitors of bone resorption by causing apoptosis in osteoclasts[207]. Lui *et al.*[152] investigated the effect of clodronate, a particular type of bisphosphonate, in rats. They found reduced tooth movement, reduced number of osteoclasts and smaller RR area. However, other studies found that bisphosphonates caused the formation of atypical hyperplastic cementum which lacks of resistance against root resorption and thus increased susceptibility to the resorptive process[208,209].

2.3.3.4.2. Dental Risk Factors

2.3.3.4.2.1. History of previous root resorption prior to orthodontic treatment

Studies have found that patients with pre-existing evidence of RR have greater risk in developing further severe OIIRR with treatment[17,19,25].

2.3.3.4.2.2. History of trauma

The history of trauma was found to contribute to apical root resorption significantly in orthodontic treatment[24,33]. Trauma itself can cause root resorption without any orthodontic force application but the combination of trauma and orthodontic tooth movement can accelerate the resorptive process[24,33].

The severity and type of trauma are also important factors with intrusive trauma being the most serious which may lead to severe root resorption and ankylosis[32].

Brin et al.[33] demonstrated that teeth with a history of trauma were more susceptible to complications such as root resorption and loss of vitality. Linge and Linge[12] found orthodontically induced average root shortening of 1.07mm with previously traumatised teeth compared with 0.64mm for untraumatised teeth. Chaushu *et al.*[210] reported 54.8% of the teeth had external resorption after intrusive trauma and all the teeth with closed root apices lost their vitality.

However, Kjaer[28] proposed that teeth with slight or moderate injuries may not lead to any greater risk of OIIRR than uninjured teeth. Moreover, it has been shown that traumatized tooth without any sign of root resorption after 4-5 months, did not resorb more than non-traumatized tooth[211,212].

Malmgren et al[212] suggested waiting for 1 year after a traumatic incident before commencing orthodontic treatment.

2.3.3.4.2.3. History of endodontic treatment

There are conflicting reports in literature on the susceptibility of endodontically treated teeth to OIIRR.

It has been suggested that endodontically treated teeth can be readily moved as vital teeth since pulp is not the key element in orthodontic tooth movement[37].

Esteves et al.[34] reported no statistical difference in apical root resorption between endodontically treated and untreated teeth. Others reported more root resorption with endodontically treated teeth than vital teeth[37]. In contrast, other studies have shown that endodontically treated teeth exhibited less root resorption than vital teeth[36,35]. Many authors believed that endodontically treated teeth were more resistant to OIIRR due to an increase in hardness and density of dentine[31,36,43,213].

2.3.3.4.2.4. Hypofunctional Periodontium

A hypofunctional periodontium has narrowed periodontal space with derangement of functional fibres which lessens the cushioning effect of PDL to distribute force.

This results in high concentration of force which leads to stimulation of inflammation and subsequent OIIRR[38,39]. Sringkarnboriboon and colleagues[40] compared the amount of root resorption associated with a normal and a hypofunctional periodontium in rats. Their results showed that the amount of root resorption was significantly greater in teeth with a hypofunctional periodontium than in those with a normal periodontium.

2.3.3.4.2.5. Alveolar bone density and turnover rate

It has been suggested that OIIRR is increased in dense alveolar bone[42,43]. In addition, a strong continuous force on low density alveolar bone caused equivalent OIIRR as a mild continuous force on high density alveolar bone[42].
Verna and colleagues [44] found high bone turnover increased tooth movement in rats. Whereas the low bone turnover group showed more RR suggesting that in subjects with a decreased or delayed bone turnover rate, root surfaces could already be affected by RR at baseline condition, thus more susceptible to further OIIRR.

2.3.3.4.2.6. Abnormal root morphology and dental anomalies

Many studies indicated increased OIIRR in teeth with aberrant-shaped roots[7,28-31]. Sameshima and Sinclair ranked the shape of roots in descending order of risk: dilacerated, pipette shaped, pointed[7]. When the same orthodontic force is applied to the root apex, the distribution of the stress is different according to the root anatomy, and the increased stresses may traumatize the apical PDL, causing an inflammatory/repair process, and progressing to resorption of the root apex[15]. Using finite element model (FEM), Oyama *et al.*[27] showed that significant stresses were concentrated at the apex with bent or pipette-shaped root. Moreover, during orthodontic force application, greater loading was observed in the short, bent, and pipette-shaped root shapes, suggesting a higher risk of resorption.

In addition to root morphology, dental anomalies such as invagination and taurodontism have been proposed as a predisposing factor for OIIRR[28,214]. However, other researchers did not identify individual anomalies as risk factor for root resorption[215,216].

2.3.3.4.2.7. Specific tooth and site susceptibility

The teeth most likely to be affected by OIIRR in descending order of severity are: maxillary lateral incisors, maxillary central incisors, mandibular incisors, distal root of mandibular first molar, mandibular second premolars, and maxillary second premolars[7,48,211,217]. Maxillary lateral incisors are most susceptible to root resorption due to the abnormal root shape[7].

Maxillary dentition is more prone to root resorption than mandibular dentition[17,169,213,218]. In particular, maxillary first premolars are more likely to suffer from OIIRR than the mandibular first premolar[219, 220]. This could be a result of greater recruitment of inflammatory cells due to the lower bone density and increased vascularisation of the maxilla and the proximity to the maxillary sinus.

In a series of 200 consecutively debanded patients, Kaley and Phillips[41] observed 3% of maxillary incisors with severe root resorption (greater than one-quarter of the root length) and 1% for other teeth. In general, it was postulated that if there is no apical root resorption detected in the maxillary and mandibular incisors, then it is less likely for significant apical resorption in other teeth[221].

2.3.3.4.2.8. Types of Malocclusion and proximity to cortical plate

There are conflicting reports in literature regarding the relationship between OIIRR and malocclusion. Some studies identified an association[4,7,24,25], while others reported no association[31, 69]. Increased overjet has been associated with greater OIIRR[7,24]. The reason for the increased RR in severe malocclusion is likely due to the more extensive treatment requirements, for example, greater retraction or excessive torque in large overjet correction, or greater intrusion in deep overbite correction[4,47]. Various reports on increased risk of OIIRR with the type of malocclusion: Cl III[41], Cl II Div1[49], Cl II Div2[222], open bite[223,25]. Cl III surgical patients had 1.6% and 20.8% reduction in maxillary and mandibular incisor length respectively[41]. This effect was possibly due to the surgery altering the blood supply and nutrition to the periodontium[162].

In addition, proximity to cortical plate has been identified as another factor in increased OIIRR. Maxillary incisor roots against the palatal cortical plate was risk indicator with an odds ratio of 20[41].

2.3.3.4.3. Mechanical Risk Factors

These factors are attributed to the mechanics of orthodontic therapy and are controlled by both the clinician and the patient.

2.3.3.4.3.1. Orthodontic Appliances

Studies have attempted to determine the appliance type and the treatment technique that minimise OIIRR. In general, fixed appliances cause significantly greater OIIRR than removable appliances[12]. This difference could be attributed to the nature of the removable appliances which do not deliver continuous force and allow tissue recovery while removed. Clear sequential removable thermoplastic appliances causes similar amount of root resorption as light (25 g) forces with fixed appliances[52].

Various studies reported that one technique is more advantageous over the other, for example, Edgewise over Begg[51,224,221], Begg over Edgewise[54], Straightwire over Standard Edgewise[53]. However, other studies found no difference between bracket types[47,54,212,218,225].

Alexander[217] found no difference in the extent of root resorption between continuous arch and sectional arch mechanics.

The use of intermaxillary elastics was identified as a significant risk factor for OIIRR[24,12,31] due to the jiggling forces that have been shown to increase the risk of root resorption[18,31,226]. However others did not detect such relationship[68].

2.3.3.4.3.2. Treatment duration

The majority of studies reported a link between the severity of OIIRR and treatment duration[30,47-50,68,70,227,228]. Only a small number of studies disagree with these findings[31,69].

Sameshima and Sinclair[68] assessed 868 patients and found duration of treatment was significantly associated with root resorption. It has been reported that 34% percent of the teeth underwent root resorption after 6-9 months of orthodontic treatment and this rate increased to 56% after 19 months of treatment duration[30]. A study on maxillary en masse anterior retraction (n=50), Liou and Chang[229] demonstrated the amount of OIIRR in maxillary incisors were significantly correlated to the duration of treatment.

2.3.3.4.3.3. Direction of force application

Different types of tooth movement is generated during orthodontic treatment depending on the direction of applied force and the moment generated: intrusion, extrusion, tipping, bodily movement, torque, and rotation. The resulting variation in the amount and location of stress concentration within the PDL is thought to correlate with OIIRR.

It has been reported that intrusion is most likely to cause OIIRR[42,230]. Han et al.[231] showed intrusion causing approximately four times more root resorption than extrusion. The extent of OIIRR from intrusion is further exacerbated by duration and magnitude of force[42,64,70,176]. In extrusive movement, Weekes and Wong[232] demonstrated OIIRR occurring at the interproximal region of the cervical third region of the root.

Bodily movement has been associated with less root resorption compared with tipping due to the difference in the stress distribution[233,234]. Studies have reported stresses concentration at the alveolar crest and the root apex during tipping movement[235-237]. Using micro-CT, Chan and Darendeliler[238] demonstrated that buccal cervical and lingual apical regions had significantly more resorption craters during buccal tipping movement. Following application of palatal root torque, an SEM study has shown RR craters on the palatal apex and buccal cervical regions[55]. In addition, Sameshima and Sinclair[68] reported that displacement of the incisor apices were significantly associated with root resorption. Root shortening due to labial root torque was quantified to be 12.7% per year[228].

The stress distribution during rotational movement is closely related to the anatomical shape of the tooth and socket. Using finite element analysis, McGuinness[239] demonstrated that the highest stress concentration areas was located in the cervical region of human canine. However, Rudolph et al.[235] reported the highest stress concentration at the apex of the root. In contrast, Wu et al.[240] showed root resorption craters mostly located at the boundaries between the buccal and distal surfaces, and between the lingual and mesial surfaces.

2.3.3.4.3.4. Magnitude of force application

Many animal[58,60,61] and human[55,56,59,241,242] studies have reported direct correlation of force magnitude with the severity of OIIRR. When heavy force is applied (exceeding 26 g/cm^2 capillary blood pressure[104]) ischeamia, hyalinization, OIIRR results and repair process is affected[42,61,64,185,230,243]. Hohmann *et al.*[244,245] showed an increased hydrostatic pressure is well correlated with the locations of root resorption for each tooth. Using a finite element model for intrusion movement, they noted that the increase in hydrostatic pressure of the PDL is the key parameter predicting root resorption[245]. Recent series of studies by Darendeliler and colleagues[52,181,238] demonstrated the force magnitude as a significant factor for the extent of root resorption with the heavy force group had 3.31-fold greater amount of root resorption than light force group[238]. In an animal study examining 10, 25, 50 and 100 g of force on rat molars, Gonzales et al.[60] demonstrated that as heavier forces were applied, greater root resorption occurred.

On the contrary, some studies indicated no correlation between magnitude of applied force and the severity of root resorption. Owman-Moll[121,179] postulated that the severity of root resorption (extension and depth of resorbed root contour and size of root area on histological sections) did not differ significantly when the applied force (50 cN) was doubled to 100 cN and increased four fold to 200cN.

2.3.3.4.3.5. Duration of force application

There are conflicting reports regarding continuous or intermittent force in relation to the OIIRR. Numerous studies demonstrated amount of OIIRR increased with the duration of the force application[64,65]. In addition, it was observed that continuous forces caused significantly more severe root resorption than intermittent forces[62,65].

On the other hand, several studies reported no correlation between the severity of OIIRR and force duration. Owman-Moll[66] noted no difference in the amount or severity of root resorption between the continuous and interrupted continuous forces of the same magnitude (50 g). Similarly, no correlation was found between duration of intrusion and the amount of resorption[67].

The effect of treatment pause was investigated by Levander et al.[63]. They assessed the effect of 2-3 months treatment pause on teeth that developed RR after initial six months of treatment. It was demonstrated that the amount of OIIRR was significantly less in the treatment pause group. The interruption of the forces facilitated the reorganisation of damaged periodontal tissues and restoration of blood flow occurs and reduced root shortening[63].

2.3.3.4.3.6. Distance of tooth movement

Teeth that are moved large distances have extended exposure to the resorptive process and also longer treatment duration. Many studies have supported this direct relationship between the severity of OIIRR and the distance of tooth movement[67-69,246,247]. The upper incisors are commonly moved the greatest distance and are at the highest risk of OIIRR[68,221,246,247].

2.3.3.4.3.7. Extraction versus Non extraction treatment

There are inconsistent reports on the relationship between the OIIRR and the extraction/non extraction treatment[51,68,70]. The nature of treatment can vary significantly with extraction treatment, for example, extraction in severe crowding will not impact on the incisor movement as much as extraction for incisor retraction purpose.

2.3.3.5. Prevention and Management of Orthodontically Induced Inflammatory Root Resorption

Vlaskalic et al[50] and Ghafari[162] summarised approaches to minimise OIIRR: reduced treatment duration[30,230], use light intermittent forces[42,64,185,230,235], habit control[17,26], avoidance of sustained jiggling intermaxillary elastics[24], limit tooth movement for teeth susceptible to OIIRR such as intrusion and torque[54], and scrutinization of medical history and familial tendency.[17,70,248]

It was strongly recommended periapical radiographs to be taken at least every year to monitor for presence of OIIRR[162]. Several other studies suggest that initial treatment periapical radiographs after 6 months[29,63,249].

If OIIRR is detected, treatment goals should be reassessed if RR is severe[250], the force level should be modified, or active treatment should be stopped for 2-3 months[63]. Additional radiographs should be taken every 3 months in at-risk patients to monitor the progress of RR[29,162]. Final radiographs are mandatory at the end of the active treatment[250]. If severe root resorption exists, follow-up radiographs should be taken every 3 months until no progress of OIIRR is detected[249]

2.4. Magnets and magnetic fields

2.4.1. Magnetic properties and types

A magnet is an object that exhibits an external magnetic field. Magnets have two poles, a north and a south pole. It has the property that like poles repel each other, and unlike poles attract[251,252]. The magnet field is a vector which has both magnitude and direction[253]. It emerges from the north pole and returns to the southpole[78]. The magnetic field strength, also known as magnetic field intensity or magnetising field, is represented by the symbol H[251]. It may be defined in terms of magnetic poles. At one centimetre from a unit pole the field strength is one Oersted. The Oersted is the unit of the magnetic field strength in the CGS system and it is measured in amperes per meter (A/m) in SI units.[251]

Magnetic flux is a measure of quantity of magnetism, taking into account the strength and extent of the magnetic field[252]. It is proportional to the total number of magnetic field lines that pass through the surface. The flux per unit area is called the magnetic flux density or magnetic induction, and is represented by the symbol B[251]. The unit of the flux density is the tesla (T) or gauss (G) where 1 gauss = 10^{-4} tesla[253]. The flux density is proportional to the magnetic field strength[251,252].

The magnetic flux produced by magnets causes them to attract or repel other magnets, and attract materials containing iron[78]. The force produced by any two magnets is inversely proportional to the square of the distance between them[251,252].

$$f \propto \frac{1}{d^2}.$$

This means that the force between any two magnets falls dramatically with distance[78]. Force-distance diagrams of magnets can be used to calculate the magnetic force level by measuring the gap between magnets[254].

2.4.1.1. Magnetisation

Magnetic fields are produced by moving charges[253]. Every atom is a magnet because electrons orbit the nucleus[255]. In most substances the electrons are paired and the magnetism produced at the atomic level tends to cancel out with the result that the substance is nonmagnetic[251,253,255].

In ferromagnetic materials, the cancellation does not occur, and have small but highly magnetised region called a magnetic domain. Often the magnetic domains are arranged randomly, so the magnetic fields of each domain cancel each other and no overall magnetism is displayed[253,255]. However, on the application of a magnetic field (H) provided by a permanent magnet or an electromagnet, the domains align and produce a state of magnetism which can be in different patterns such as axial and radial[253].

In some types of ferromagnetic materials the domains remain aligned when the external magnetic field is removed, and the material becomes permanently magnetised (Br). The magnetisation can be reduced to zero by the application of an equal and opposite magnetic field. By continuing to increase the magnitude of the reversed field, the material can be again saturated, but in a negative value[251,256].

2.4.1.2. Magnetic properties of matter

There are three different types of magnetic substances: diamagnetic, paramagnetic and ferromagnetic substances[251,253].

Diamagnetism causes lines of magnetic flux to curve away from the material and creates a magnetic field in opposition to the externally applied magnetic field, a repulsive effect. A diamagnetic substance is weakly repelled and exhibits no permanent magnetism. They include water, wood, most organic compounds and many metals such as bismuth, silver, gold, lead, stainless steel and copper[251].

Paramagnetism is a form of magnetism which occurs only in the presence of an externally applied magnetic field. A paramagnetic substance is one that is weakly attracted to magnets, and therefore will exhibit a small increase in magnetic flux density when an external magnetic field is applied. Iron and rare-earth salts are paramagnetic substances, as well as elements such as sodium, potassium and oxygen.

A ferromagnetic substance is one that is strongly attracted to magnets. The magnetic domains are parallel in a ferromagnetic material. Common ferromagnetic materials are iron, nickel, cobalt, chromium dioxide and alnico, an aluminium-nickel-cobalt alloy[253]. Ferromagnetic materials can be termed as either hard or soft depending on how well they retain their magnetic properties after removal of an applied magnetic field[251,255,256]. A soft magnet can be easily magnetised or demagnetised[251], for example, iron. A hard magnet is able to retain magnetic properties after being magnetised and can be made into permanent magnets[255].

2.4.1.3. Permanent magnets

Permanent magnets create their own persistent magnetic field[251]. All permanent magnets are made from ferromagnetic materials[253].

The Curie temperature (Tc) is the temperature at which any ferromagnetic material loses its magnetism. Above this temperature, thermal agitation destroys the magnetic alignment and the magnet become demagnetised[78,256].

2.4.1.3.1. Alnico magnets

Alnico magnets were the first type of permanent magnets to be used for biomedical purposes[256]. Alnico magnets are alloys based on cobalt, aluminium, nickel and iron[255,257]. These magnets were developed from the 1930s to the 1960s and offered considerable improvements in magnetic hardness compared to the steel magnets that were previously available[256].

2.4.1.3.2. Cobalt-platinum magnets

Cobalt-platinum magnets were available at the same time as Alnico magnets. They were discovered in the 1930s and became available in the 1950s[256,257]. They consist of equal percentages of cobalt and platinum, and had improved properties and corrosion resistance. They did not gain widespread use in medical or dental applications because of their high cost[256,258].

2.4.1.3.3. Ferrite magnets

Ferrite or ceramic magnets are the most widely used permanent magnetic material and play an important role in bulk magnet applications[251]. Hard ferrite magnets are not commonly used in biomedical applications[256].

2.4.1.3.4. Rare earth magnets

Rare earth magnets are capable of producing high forces relative to their size due to the property of magnetocrystaline anisotrophy[78,259]. This property allows single crystals to be preferentially aligned in one direction (along the C-axis) which increases the magnetism[259]. The rare earth magnets demonstrate significant improvements in the maximum energy product (BH_{max}) which has lead to a dramatic reduction in the size of magnets required to produce a particular magnetic flux[78,255]. They have very high coercivity, that is, a superior ability to resist demagnetisation.

There are several types of rare earth magnets – samarium cobalt, neodymium iron boron and samarium iron nitride[256].

2.4.1.3.4.1. Samarium-Cobalt magnets

Samarium-cobalt (SmCo) magnets were developed in the 1960s and 1970s[260,261]. These magnets are characterised by high saturation magnetisation and Curie temperature (500-750 °C)[260]. They are more costly than other rare earth magnets but are chosen in preference to those with a lower Curie temperature when they are needed for high temperature applications[256].

2.4.1.3.4.2. Neodymium-iron-boron magnets

Neodymium-iron-boron (NdFeB) magnets were first announced in 1984[262,263]. It has an extremely high magnetic saturation, good resistance to demagnetisation and the highest value of energy production. Their excellent magnetic properties allow the production of very small magnets[78]. They are the main rare earth permanent magnet in use today[256].

The main limitation of the neodymium magnet is that it had a low Curie temperature, as low as 300°C[261,262]. This is a distinct disadvantage for dental applications as magnets are embedded in acrylic appliances which reaches a temperature of 80- 90 degrees on curing[78]. This could cause a significant amount of flux loss.

2.4.1.3.4.3. Samarium-iron-nitride magnets

Samarium iron nitride permanent magnets are a promising candidate for future applications[255]. These magnets have high resistance to demagnetisation, high magnetism and better resistance to temperature and corrosion[255].

2.4.2. Biological considerations

Biological safety tests of magnetic materials have been performed to investigate the effects of static magnetic fields and possible toxic effects of the materials or their corrosion products[77,78]. Several studies have shown that magnets have good biocompatibility[264-267]; however, cellular changes in response to static magnetic fields and corrosion products have been documented[268].

2.4.2.1. Surface oxidation and coating

Rare earth magnets, especially those containing neodymium, are known to be susceptible to corrosion[267,269,270]. Without a coating material oxygen diffuses into the magnet causing a metallurgical change in the surface layer. It is recommended that they are hermetically sealed for dental use[267,269,271].

In vitro studies investigating the effects of the corrosion products reported a range of effects from "no cytotoxic effects"[267,272,273] to "mild cytotoxic effects"[268,269]. Investigation of the short term effects of NdFeB magnets on osteoblast-like cells (UMR-106) did not appear to have any cytotoxic effects. Papadopulos et al.[273] also did not show any significant effect on cellular activity in either attractive or repulsive magnetic fields.

Coating materials, such as biocompatible epoxy resin[72], stainless steel[274] or a thin layer of parylene[71], are designed to act as a barrier to corrosion. Bondemark et al. reported that small amounts of water-soluble cytotoxic components were released by partially stainless steel coated samarium-cobalt magnets[269]. Vardimon and Mueller[270] stated that acrylic alone was not an adequate coating material. Parylene (poly-para-xylene) is not sufficient to survive undamaged in the intra-oral environment.

The use of coating materials is also advocated to preserve the magnetic properties and clinical usefulness of intra-oral magnets[264,275,276]. Disturbance of the physical properties and tarnishing of the magnets can occur after the corrosion assault[264]. Drago[277] reported that tarnish and corrosion can seriously compromise the long-term effective use of intraoral magnets.

2.4.2.2. Static magnetic fields

Controversy exists in the literature with respect to the effects of static magnetic fields produced by the size and type of magnets used in orthodontics[78,264].

The effects of magnetic fields on the growth of cell cultures, both animal and human, have been evaluated. *In vitro* tests have demonstrated that static magnetic fields can affect certain biological parameters, such as stimulate enzymes, cell proliferation and attachment and osteogenesis[78,278-280]. Also, there was release of cytotoxic components from new and clinically used magnets[269].

The reported effects of magnetic fields on the growth of human cells are inconsistent. Some studies show no significant effects with regard to DNA synthesis, DNA content, cell shape, structure and number[281] or glycolytic activity[282]. Whereas, Linder-Aronson and Lindskog showed progressively impaired attachment and cell growth. However, they did not exclude the possibility of corrosion products from the magnets contributing to the cytotoxic effects[280].

Animal tests reported no adverse effects in the blood cells[283], the tissues surrounding the implants[265,284], and the dental tissues[266]. *In vivo* studies on rats and monkeys demonstrated a reduction in epithelial thickness with permanent rare-earth magnet exposure. No abnormal healing or osteoblastic activity were detected after implantation of titanium-coated SmCo magnets in dog mandibles[285] and in rabbits[286].

Darendeliler et al.[287] examined the effects of static magnetic fields (SMF) and pulsed electromagnetic fields (PEMF) on the rate of tooth movement and showed a significant increase in the rate of tooth movement. Both experimental groups experienced a reduction in the lag phase between the third and sixth day. Blood chemistry showed a reduced serum level of calcium, which was related to an increased rate of osteogenesis and an increase white blood cell count, possibly as a reaction to corrosive products[287]. In a related study Darendeliler *et al.* investigated the effects of SMF and PEMF on the rate and quality of hard tissue repair after osteotomies in guinea pig mandibles. Wound healing was found to be faster in both groups compared to the controls[288].

Bondemark et al.[289] examined human buccal mucosa after nine months exposure to orthodontic NdFeB magnets. Examinations clinically, histologically and immunohistochemically found no adverse long term effects on human buccal mucosa in contact with an acrylic-coated neodymium iron boron magnets. In addition, Bondemark et al.[290] found that the SMF produced by rare earth magnets for orthodontic use did not cause any change in human dental pulp or gingival tissues adjacent to the magnets[290].

2.4.3. Application of magnetic forces in orthodontics

Magnetic forces have been used in orthodontics for both tooth movement[71-75] and orthopaedic correction[291-296]. The use of magnets for generating orthodontic forces has been a subject of increasing interest[77,78,297].

Traditional force delivery systems in orthodontics utilise wires, elastics and extra-oral devices[298,299]. Advantages of magnetic force delivery reported in the literature include good force control over short distances, no friction and no material fatigue[297]. Magnetic systems permit precise control of the force levels that are applied as they can be calculated from specific force-distance diagrams by measuring the distance between magnets[297].

Several animal and clinical studies have documented the reliability of using magnetic forces for different tooth movements as summarised in the sections below.

2.4.3.1. Molar distalisation

Several authors have reported on the use of magnets to move molars distally[73-75,300-302]. In 1988 Gianelly et al described a new intra-arch method, whereby distalisation of maxillary first molars was achieved with repelling magnets in combination with a modified Nance appliance cemented on the premolars[74]. The molars were distalised at a rate of 0.75-1mm per month, without significant anchorage loss (20 percent)[73]. Bondemark and Kurol using an analogous system to generate a repelling force of 116 grams at 1mm separation reported a mean crown movement of 4.2mm, 8 degrees of distal tipping and 8.5 degrees of disto-buccal rotation in ten consecutively treated cases[300].

Bondemark et al. compared the effectiveness of repelling magnets versus superelastic nickel titanium coils in maxillary first and second molar distalisation over a 6 month period[75]. Mean distal molar movement was greater for the coils than the magnets, 3.2mm compared to 2.2mm. Erverdi conducted a similar study (with weekly activation of the magnets) also reported nickel-titanium coils to be more effective[301].

Bondemark and Kurol later evaluated radiographically the impact of these treatment techniques on proximal alveolar bone level changes. The authors concluded that there was no difference between an interrupted continuous force system produced by a magnet and a more continuous force produced by the superelastic nickel-titanium coils[303].

2.4.3.2. Extrusion

Attractive magnets have been used for orthodontics to extrude a traumatised incisor and enhance root eruption[304, 297]. The appliance comprised of one magnet fixed to the root and one embedded in a removable partial denture. To achieve rapid extrusion, forces of 50 to 60 cN are recommended, approximately twice as much as that required for normal extrusion of a single rooted tooth[305]. The roots were successfully extruded 2 to 3mm with a force range from 50 to 240 cN during a treatment period of 9 to 11 weeks.

2.4.3.3. Impacted teeth

Treatment options for the management of impacted teeth include extraction, transplantation, and surgical exposure alone[299]. Conventional treatment of impacted tooth involves bonding the exposed tooth with mesh and chain and place orthodontic traction through mucosa, and it has associated problems such as gingival inflammation, reduced attached gingiva and difficulty in control traction force level[71,306].

An alternative employs magnetic traction. It involves surgical exposure of the impacted tooth, after which a magnet is bonded to the tooth surface. The mucosal flap is sutured in place, completely covering the tooth with its bonded magnet. Guided eruption is achieved by means of a second magnet embedded in an appliance and placed in such a way as to attract the sub-mucosal magnet into the ideal place. As the eruptive process is through normal, closed mucoperiosteum it has been stated that this ensures that a healthy periodontium will surround the tooth[307].

The technique has been applied to the eruption of incisors, canines, premolars and molars[71,308-310]. Darendeliler and Friedli combined the use of removable and fixed attraction systems for an impacted canine. The fixed component consisted of a magnet-fixed Ballista type sectional arch. The authors did not observe any side-effects and concluded that the use of magnets was effective for the eruption of impacted teeth and that treatment time and discomfort were reduced[306].

The reported advantages of guided eruption include: operator and patient ease as there is no need to attach hooks or elastics, reduction in adjustments, continuous forces over a long period of time, friction-free system, healthy periodontium as the eruptive process is through normal, closed mucoperiosteum and reduced risk of infection[78,307,308,311]. However, there are a number of limitations with this approach: attractive forces fall rapidly as distances between the magnets increase, the magnets may be subject to corrosion if the coating is damaged and care must be taken to ensure the correct polarity of the magnets[78].

2.4.3.4. Retention

Micro-magnetic retainers were introduced by Springate and Sandler in 1992[312]. In their case report small (0.8x0.8x1.5mm), NdFeB magnets were bonded to the palatal surfaces of the upper central incisors to prevent a median diastema from opening[312]. Directly bonded magnets have advantages over conventional fixed retainers. Oral hygiene can be maintained as flossing is not prevented and there are no wires close to the gingival margins. The teeth are not splinted which allows normal physiological movement. However, there are potential problems with this approach. The magnets can debond and the friction between the magnets may cause damage to the protective resin coating and expose the magnet which will corrode[78].

3. RESEARCH METHODOLOGY

3.1. Mach-1 universal testing machine

The Mach-1universal testing machine (Biosyntech Inc, Quebec, Canada) was used to measure the attractive force of pairs of magnets. An electric motor and computerised system allows vertical displacement of the upper component of the machine while the lower component of the machine maintained stationary. Magnets are attached to a non-magnetic aluminium customised mounting jig using a small amount of adhesive (Loctite® Super Glue Gel Control ™, Henkel, Düsseldorf, Germany). A 10kg load cell was calibrated and the force measurement (in grams) was commenced with the magnetic pair in contact and then vertically separated 10mm at a speed of 12mm/min. The start position (0µm) was determined as the position corresponding to the peak tensile force (the "breakaway" load).

3.2. X-Ray Microtomography

Limitation of the conventional radiographs is that the production of a two dimensional image from a three dimensional object.

Tomography produces a two dimensional map of X-ray absorption in a two dimensional slice of the subject. A series of X-ray projections are made through the slice at various angles around an axis perpendicular to the slice. From this set of projections the x-ray absorption map is computed, and by taking a number of slices, a three dimensional map is produced[313].

Four generations of computed tomography that have been classified in the literature. The first generation or known as pencil beam system has the simplest arrangement composed of the X-ray source, a pin hole collimator and a single detector as designed by Hounsfield[314]. The second generation uses a parallel beam of X-ray; while, third generation uses a flat fan distribution of X-rays. The fourth generation of computed tomography scanning device uses a cone beam geometry, which is a three dimensional analogue of the two dimensional fan beam geometry[315]. This design is ideal for volumetric computed tomography.

The resolution of a two dimensional image is given in terms of pixels. A pixel is a two dimensional representation of the smallest unit of colour value within an image. This value can be a shade of grey or colour. The quality of an image improves with a greater resolution, i.e. the more pixels per unit area.

In three dimensional terms, the term voxel is used. A voxel is a three dimensional modification of a pixel with the added dimension of depth. Thus, a voxel has a volume and its dimensions have an X, Y and Z axis.

Skyscan 1172 is a compact desktop system for microscopy and micro tomography. It consists of an X-ray shadow microscopic system and a computer with tomographic reconstruction software. The system allows the researcher to make a non-destructive three dimensional reconstruction of the object's inner structure from two dimensional X-ray shadow projections. A spatial resolution of 5 micron corresponding to near $1x10^{-7}$ cubic mm voxel size can be produced.

The system obtains multiple X-ray shadow transmission images of the object from different angular views, as the object rotates on a high precision stage. From these shadow images, cross section of the object are reconstructed by a modified Feldkamp cone beam algorithm, creating a complete 3D representation of the internal microstructure and density over a selected range of heights in the transmission image. After the serial reconstruction, three dimensional image displayed can be cut into cross sections, rotated and internal morphological parameters can be calculated. The sample is placed on a rotating platform which is programmed to revolve over 180 or 360 degrees with a fixed rotational step. The distance of the platform from the X-ray source determines the magnification. A higher magnification gives greater detail. A high resolution charged coupled device with a resolution of 1024x1024 pixels detects the incoming X-ray. The images are received and stored as 16 bit Tagged Image File Format (TIFF) picture files with a resolution of 1024x1024 pixels. The software package, VG Studio Max v1.2, v.2.1 and v2.2 (Volume graphics GmbH, Heidelberg, Germany) is used to collate all the axial slices to form a three dimensional reconstruction of the scanned image.

3.3. Use Of Palatal Rugae and Orthodontic Tooth Movement

The palatal rugae is located on the anterior half of the hard palate and do not extend beyond this point posteriorly or cross the midline. The shape, length, width, prominence, number and orientation of the palatal rugae vary considerably among the individuals[316 317].

Some recent investigations have evaluated the stability of the palatal rugae during growth and orthodontic treatment[318-322]. In the comparison of tooth movement measured by cephalometric superimposition relative to the rugae points on study models, the medial points of the third palatal rugae are suggested to be suitable reference points for the assessment of anteroposterior tooth movement[321,322]. In contrast, the lateral points of the third rugae are reported to be the most stable in another study.[318,322].

In this study, the first three palatal rugae were used to superimpose the models.

3.4. 3 Dimensional Laser Surface Scanner

Conventional radiographic method of tooth movement evaluation involved a two dimensional reflection of a three dimensional object. It has certain limitations such as, blurring, overlapping of anatomic structures, magnification error, as well as inevitably subjecting patients to radiation exposure. With the development of

3D measuring devices, some investigators have performed 3D superimposition of dental casts to analyze orthodontic tooth movement[319,322-324].

Digital 3D models are fast becoming a standard technology[324]. Numerous studies have shown that 3D digital models can be used for model analysis and diagnosis[324-326] [327] [328,329], treatment planning[330,331], design and manufacture of orthodontic appliances[332-334], and evaluation of tooth movement[335] [322,324,336]. However, studies on the reliability of computed superimposition of 3D digital models to assess the outcomes of orthodontic treatments have been limited[322,335].

OpenScan 100 Laserdenta is a specifically designed device for dental use. This scanner provides a resolution as high as 20 micron (0.02 mm) in each scan. Surface Tesselation Language (STL) formatted files then were then processed with VG Studio Max version 2.1 (Volume Graphics, Germany)

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5. MANUSCRIPT

The Extent of Root Resorption and Tooth Movement Following the Application of Ascending and Descending Magnetic Forces: A microcomputed-tomography Study

This manuscript is to be submitted to the American Journal of Orthodontics and Dentofacial Orthopedics.

The extent of root resorption and tooth movement following the application of ascending and descending magnetic forces: A microcomputed-tomography study

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5.1. Abstract

Intruduction: Various factors have been examined in the literature in an attempt to reduce the incidence and severity of root resorption. The objective of this study was to investigate the effect of ascending and descending force (generated by magnets) on root resorption. **Methods:** 20 maxillary first premolars from 10 human were subjected to ascending (25 to 225g, magnets in attraction) and descending (225 to 25g, magnets in repulsion) buccal forces using a split mouth design over a 8 week period. PVS impressions were taken at week 0, 4 and 8 to record the tooth movement. After 8 weeks, the teeth were extracted, scanned with micro-CT in 16.9 µm resolution, and the root resorption craters were localised and quantified. **Results:** The total volume of root resorption with ascending force was 1.20 mm^3, and with descending force was 1.25 mm^3, and there was no statistically significant difference between them. The root resorption on the palatal surface (0.012 mm^3) was significantly less than on the buccal surface (0.057 mm^3) and than on the mesial surface (0.035 mm^3). The vertical locations (cervical, middle, and apical) showed no statistically significant difference in root resorption. The amount of tooth movement after ascending and descending force application was not statistically significant. **Conclusions:** Orthodontic ascending and descending forces, from 25 to 225 grams and from 225 to 25 grams respectively, do not cause different amount of root resorption or tooth movement following eight weeks of force application.

5.2. Introduction

Orthodontically induced inflammatory root resorption (OIIRR) is the pathological inflammatory process that results in loss of mineralised cementum and dentine concurrent with removal of hyalinized tissue[1-3]. This phenomenon is due to the overcompression of the periodontal ligament (PDL) which results in aseptic coagulation necrosis process (hyalinization). OIIRR has been demonstrated to be influenced by a variety of mechanical and/or biological factors. The biological and environmental factors include: genetics[4,5,6], ethnicity[7,8,9], endocrine imbalance[10,11], asthma[12,13], medications[14,15,16,17,18], nutrition[19], alveolar bone density and turn over rate[10]. In addition, mechanical factors include the type of orthodontic appliance[20,21], treatment duration[22-30], direction of force application[31,32,33], magnitude of force application[34-38], duration of force application[39,40], and, distance of tooth movement[40,28].

In particular, orthodontic force magnitude has been shown to be a major factor in OIIRR in many animal[18,41,42] and human[34-38] studies. Light forces have been recommended to reduce adverse tissue reactions[2,43,44]. In addition, recent series of studies by Darendeliler and colleagues[21,45,46] demonstrated the force magnitude as a significant factor for the extent of root resorption with the heavy force group having 3.31-fold greater amount of root resorption than light force group[46]. In contrast, some other studies proposed no relationship between force magnitude and severity of OIIRR[47,48].

The relationship between force magnitude delivered by orthodontic appliances and the rate of orthodontic tooth movement remains controversial. According to Quinn and Yoshikawa, the rate of tooth movement is related to the force magnitude applied[49]. In a human study, heavy force application demonstrated an increased amount of tooth movement in canine distalisation[50]. In contrast, it was also shown that light force produced more tooth movement after 28 days[18]. However, others proposed that there is no or direct relationship between force magnitude, type of tooth movement, and amount of displacement[51,52]. Using a mathematic model, Ren et al concluded that no optimal force nor force range could be calculated to produce maximum tooth movement[53]. Variables previously mentioned, such as alveolar bone density, force magnitude, direction, distribution and duration need to be considered in obtaining optimal tooth movement.

Magnets have a wide range of application in orthodontics such as: intrusion[54,55], expansion[56-58], tooth impaction[59-61], and functional appliances[62-65]. In addition, magnets have been used in orthodontic tooth movement during complex intra and inter-arch mechanics[66], molar distalisation[67,68], without arch wires[69], and as magnetic edgewise brackets[70,71].

Force consistency and continuity are vital in an optimal orthodontic force system[72]. Apart from superelastic NiTi, orthodontic force application decreases with time and tooth movement. Using magnets, it is possible to deliver gradual and smooth change in force magnitude, with the force produced by the magnets inversely proportional to the fourth root of the distance between them[73]. In addition, magnets deliver predictable force levels with no loss of force and provide frictionless mechanics[74,75].

Many studies have reported OIIRR using different type of orthodontic appliances. In the current literature, the two studies investigating the effects of magnets on tooth movement and root resorption were done on rats[76,77]. However, currently there is no reported human studies of RR utilising ascending and descending forces using magnetic appliances.

The aim of this study was, therefore, to investigate the amount of OIIRR and tooth movement using ascending and descending forces generated by magnets.

5.3. Material and Methods

Twenty maxillary first premolar teeth were collected from 10 patients (7 females, 3 males, mean age 15.8 years; range 14.5 – 17.4 years) who required extractions for orthodontic purposes at the University of Ondokuz Mayis, Samsun, Turkey. Ethics approval was obtained from the University of Ondokuz Mayis Medical Faculty Ethics Committee and from the Human Research Ethics Committee at the University of Sydney (ethics approval numbers EK:273 and X09-0277 respectively). The subject selection criteria were in accordance with previous studies in the department[78]: 1) requiring the removal of bilateral maxillary first premolar teeth as part of orthodontic treatment, 2) similar minimal crowding on each side of the maxillary arch, 3) no craniofacial anomalies, 4) no significant medical history or medication that would adversely affect the development or structure of the teeth and jaws and any subsequent tooth movement, 5) no previous orthodontic or orthopaedic treatment, 6) tooth is vital, in normal function, and not previously restored, 7) no history of trauma, bruxism, or parafunction, and 8) no past or present signs and symptoms of periodontal disease. Written informed consents were obtained.

The subjects' upper first molars were bonded with a passive trans-palatal arch (Fig. 1, Fig. 2A). This provided an anchorage so the tooth movements are fully expressed on the experimental teeth, the first premolars. The acrylic on occlusal surface of molars acted as occlusal stop to prevent occlusal interferences. A full dimension stainless steel cantilever wire extended from the molar buccal tube to the region of the first premolar with a magnet attached at the end. Another magnet was attached onto the buccal surface of the first premolar. The magnets were of circular shape with a hollow centre to allow the passage of a guiding pin. The magnets used in this study were neodymium-iron-boron magnets (Nd-Fe-B, AMF Magnetics, Sydney, Australia) with Nickel and Copper coating (15-20 µm). Using the Mach-1universal testing machine (Biosyntech Inc, Quebec, Canada) with a 10 kg load cell and a customised mounting jig, force measurement (in grams) was commenced with the magnetic pair in contact initially and then the magnets were vertically separated 10mm at a speed of 12mm/min. The magnets utilised in this study had the following dimensions: Outer Diameter = 5mm, Inner Diameter = 1mm, and Height = 0.75mm (Fig. 2B). These magnets produced the force magnitude ranging from 25 to 225g as depicted by the force-displacement graph (Fig. 3).

The ascending or descending force was produced by the polarity of magnets in attraction or repulsion. On the premolar tooth with ascending force exerted upon it, the magnet attached to the tooth surface had the opposite magnetic pole to the magnet attached to the cantilever arm which acted as the reference point (Fig. 2D). On the premolar tooth with descending forces exerted upon it, the repulsive force was generated by magnets in the same polarity. The magnet was connected to the premolar tooth via the pin which was positioned exterior to the cantilever arm. As the exterior magnet was repulsed from the magnet on the cantilever arm, the distance between the magnets increased as the premolar tooth moved bucally closer to the cantilever arm, thus the force magnitude decreased (Fig. 2C).

The subjects were assessed every 4 weeks to ensure the experimental appliances were in good condition. In addition, maxillary arch impression with poly vinyl siloxane material (Imprint II Regular Body/Light Body, 3M ESPE, St Paul, Minn) was taken at three time points: Week 0 (appliance placement), Week 4 and Week 8 (appliance removal). Impressions were poured with die stone (Vel-mix, Kerr, Orange, Calif). The casts were scanned with OpenScan 3D Laser Scanner (Laserdenta, GmbH Germany). Stable palatal reference points [79,80] and the buccal and lingual cusp tips of the first premolars were marked on digitized models with VG Studio Max v.2.0. This scanner provides a resolution as high as 20 micron (0.02 mm) in each scan. Surface Tesselation Language (STL) formatted files then were superimposed by matching the reference points in three dimensional space (Fig.4). The rate of tooth movement was determined by the measuring buccal and palatal cusps movements separately and averaging (Fig.4) Each measurement was repeated 4 times and the mean value was calculated for each sample.

After 8 weeks of experimentation, the first premolar teeth were extracted carefully to prevent surgical trauma to the root cementum. The extracted teeth were immediately stored in labelled containers containing sterilised deionized water (Milli Q, Millipore, Bedford, Mass) which was previously demonstrated to be suitable storage medium[81]. Each tooth was placed in ultrasonic bath for 10 min to loosen all traces of residual periodontal ligament and soft tissue fragments which were subsequently removed by a dampened gauze with a rubbing motion. The teeth were then disinfected in 70% alcohol for 30 min and bench dried at ambient room temperature (23^0C $\pm 1^0$C) for 24 hrs.

A desktop X-ray micro-tomography system (SkyScan 1172, SkyScan N.V., Aartselaar, Belgium), capable of achieving near 1 x 10^{-7} cubic mm voxel size, was used to scan each tooth. Prior to scanning the teeth, a new Flat Field Reference was acquired to correct for sensor non–uniformity and ensures the sensor is in optimal working condition. Teeth was rotated over 360^0 at 0.2^0 rotation steps, scanned with X-rays at a voltage of 100 keV and 100 µA current. The high camera resolution setting produce an image matrix of 1500 x 1048 pixels, 1800 projections, frame averaging of 4, and random movement amplitude of 20 lines on the camera. In addition, Geometrical correction, Median Filtering, and Flat Field Correction were applied. A 1.0mm thick aluminium filter was placed infront of the detector and the resulting X-ray energy spectrum had an effective mean energy of approximately 60 keV.

The resulting 2D shadow/transmission images (16 bit TIF) were used to reconstruct the 3D object by using a 3D cone beam reconstruction algorithm (NRecon, Version 1.4.2). Beam hardening artifact was corrected by preselecting a correction level that minimized the artifact shown in the preview image, typically a value of 70 to 80 in the NRecon software was chosen. A resulting dataset of isotropic 16.9 µm voxel size resolution was achieved. Data was maintained at 16 bit TIF information.

For visualisation and analysis of three dimensional/volumetric data, VGStudio Max 1.2 (Volume Graphics GmbH, Heidelberg, Germany) was used to analyse root resorption craters. The root surfaces on buccal and lingual aspects will be divided into three levels (cervical, middle, apical). Positive identification of craters was confirmed by scrolling through axial and Sagittal slices. The resorption craters was located individually, isolated by limiting coordinates in 3 planes of space in VGStudiomax (Fig. 5). The data was then exported to convex hull software (Chull 2D, developed by Dr Allan S. Jones at the University of Sydney) to provide a direct measure of the concave volume of the 3-dimensional data set.

Statistical analysis

SPSS version 18 (SPSS, Chicago, Illinois, USA) was used for statistical analysis. A general linear model was used to investigate the differences in total root resorption between subjects using ascending and descending forces. Further comparisons were undertaken using the position on the tooth as another factor. The analysis was carried out using the cube root of the total volume of root resorption as the response variable in order to satisfy the statistical assumptions required for application of these techniques. It essentially measures the amount of resorption by the radius (mm) of an equivalent hemispherical crater rather than by the volume in mm^3 and has been employed by this research team in previous studies[32,46].

The analyses included the subject as a random factor; and the force, surface, and height as the fixed factors. The paired *t*-tests were used to determine the significance of intraindividual differences in root resorption between ascending and descending forces. The differences in tooth movement between ascending and descending forces were also examined by paired t-tests.

25% of sample was rescanned and the standard error of measurement for root resorption crater volumes was less than 2% of the actual mean measurement.

5.4. Results

The reconstructed 3D image of premolar tooth in Figure 5 shows detailed topography of root surface with resorption craters.

Ascending and descending forces produced root resorption in all teeth. The total mean volume of root resorption with ascending force was 1.20 mm^3, the descending force was 1.25 mm^3, and there was no statistically significant difference between them (Fig. 6 and Table I). The power analysis shows a 90% power of finding a difference of 0.24 (on cube root scale), and a 75% power of finding a difference of 0.20. These differences were much larger than the differences of 0.03 detected in this study. That is, the study sample size was large enough to detect 0.24 difference if it really does exist, and the study result of 0.03 difference was likely just chance.

Using an ANOVA model for crater volume (crt vol) with surface, height and side as fixed factors and subject as random factor, there was no significant effect of side (ascending vs descending, p=0.11, Fig.6, Table I) or height (cervical, middle, and apical, p=1.00, Fig. 6, Table II). The surface was marginally significant (p=0.04) with the palatal surface significantly less than on the buccal surface and mesial surface (Fig. 7, Table III).

After 4 weeks of application of ascending and descending forces, the tooth movement was found 0.94 ± 0.33 and 1.00 ±0.39 mm, respectively. At 8 weeks, the total tooth movement was 1.40 ± 0.46 and 1.74 ±0.53 mm, respectively (Fig. 8). However, there was no significant difference between the groups (diff=0.34 p=0.136).

Using a power analysis, it shows that there is a 24% power of finding a difference of 0.34mm significant, and a 94% power of finding a difference of 1mm significant in cube root scale. That is, if the real difference between ascending and descending force was 1mm, then we would have 94% power of finding it, therefore, this study sample was large enough to detect a 1 mm difference if it really does exist. In this study we found 0.34mm difference, i.e. approximately one third of 1mm difference, therefore it is likely the difference was just chance.

5.5. Discussion

Extensive research on RR, the inevitable side-effect of orthodontic treatment, encompasses the common goal of employing the most efficient and effective force application to create desired tooth movement whilst causing minimal RR. Direct correlation of the magnitude of orthodontic force applied and the severity of root resorption had been demonstrated[36,46]. The force magnitude in the initial phase of tooth movement is important because significant environmental changes occur[82]. And the general consensus in the literature recommend continuous light force, that is, tooth movement by frontal resorption with minimal hyalinized or necrotic changes associated with root resorption[1].

The different characteristic changes in magnitude of the force were considered to be a factor that may contribute to the extent of RR. The effects of increasing or decreasing orthodontic forces, which are possible by the use of magnets, on RR and tooth movement have not previously been investigated in humans. This study identified the presence of OIIRR craters on human premolar teeth after application of either ascending or descending forces, and root resorption craters were quantified using micro-CT. Our study demonstrated that the volume of RR for both ascending (1.20 mm^3) and descending (1.25 mm^3) force application sides were comparable, and there was no statistically significant difference between them. This finding is comparable to Owman-Moll[47,48], who postulated that the severity of root resorption (extension and depth of resorbed root contour and size of root area on histological sections) did not differ significantly when the applied force (50 cN) was doubled to 100 cN and increased four fold to 200cN.

The root resorption seen on the descending force side was not surprising as the initial force levels were similar to that of our previous studies using heavy forces[33]. However the results of our ascending force side is in contrast to the animal study in rats which demonstrated effective tooth movement using increasing magnetic force with no pathological changes such as RR[76]. Using magnets initially placed apart, it was postulated that ascending forces, as the force levels would start off light, would induce the smooth progression of tooth movement by frontal resorption, before the gradual increase in force magnitude as the magnets move closer together[76]. However, as magnets move closer, force levels might reach levels above physiological limits in ascending force design (Fig.3); which might explain the similar extent of root resorption observed for ascending and descending force sides in our study, comparable to that of RR values found in previous heavy force studies[21]. One possible explanation for the similar root resorption craters between the ascending and descending force is because the higher end of the force range in both ascending (25 to 225g) and descending (225 to 25g) groups highly exceed the capillary blood pressure (20-25g/cm^3)[83]. As a result, both groups were subjected to high level of force during the experimental period and that caused periodontal ischemia and subsequent root resorption.

Significantly more RR on buccal surface than palatal surface was observed in this study. This was consistent with the buccal tipping movement with the cervical region of the buccal surface and the apical region on the palatal surface being the pressure areas of buccal tipping movement[33]. This might also explain the difference in the results of the study by Tomizuka et al. (2006), as they have looked at resorption craters from horizontal microCT sections 1.0 mm ±1.0 mm above or below from root furcation.

In this study, the difference in tooth movement between the ascending and descending force groups was not statistically different in both time points (week 4 and 8). Another human study assessing tooth movement under light and heavy forces demonstrated that the force magnitude was not related to the amount of tooth movement in the initial experimental period (weeks 0-4); however, heavy force application was associated with increased amount of tooth movement in the later periods (weeks 5-8 and weeks 9-12)[50].

On the contrary in an animal study on rats comparing the amount of tooth movement with light and heavy forces, the initial tooth movement (until day 3) was not found to be different; however, from day 4 to 28, the molars have moved forwards significantly more in the light force group compared to the heavy force group[18,84]. Using beagle dogs and skeletal anchorage, it was reported that molar moved faster with 300 cN than with 10 cN; and that, the effect of force magnitude on tooth movement had a positive dose-response relation only in the very low force range, and at higher force ranges (600 cN), no effect could be established[85].

As our study design included ascending and descending forces, the force reached high levels either at the initial stage for descending force group or towards the later stages in the ascending force group, which then might have affected tooth movement in both groups during different stages.

A number of contributing factors may have influenced the minor and statistically non significant differences in OIIRR and tooth movement between the ascending and descending force groups observed in this study. The duration of treatment (8 wks) and the distance of tooth movement (buccal tipping) in this study may not be sufficient to detect the presence of potential differences between ascending and descending forces. In addition, as previously mentioned, the force range of both groups produced high force level during the experiment. Future studies could employ longer treatment duration and larger tooth movement range (such as distalisation after extraction) and reduced heavy force levels.

5.6. Conclusions

When ascending and descending forces were applied in a buccal direction to the maxillary first premolars for 8 weeks, the following conclusions were drawn.

Orthodontic ascending and descending forces, from 25 to 225 grams and from 225 to 25 grams respectively do not cause different amount of root resorption or tooth movement following eight weeks of force application. Application of either ascending or descending orthodontic forces using magnets had comparable RR to other conventional orthodontic force application systems.

Acknowledgements

We thank the Australian Society of Orthodontists Foundation for Research and Education for their financial assistance of this research.

5.7. References

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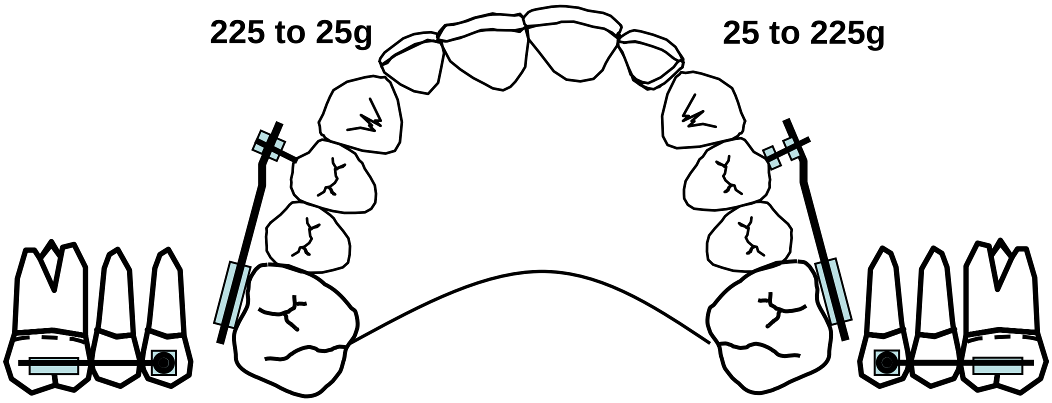
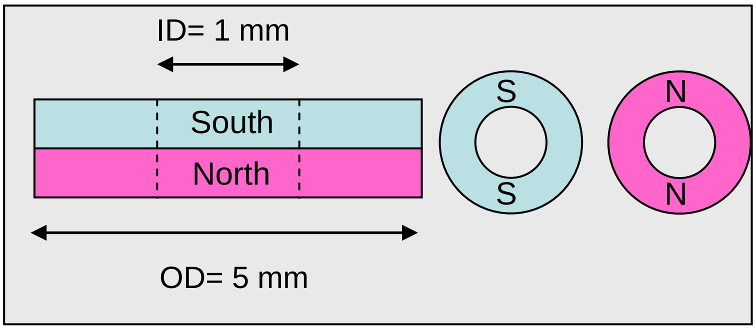
5.8. Figures and Tables

A **B** **C**

Figure 1



A



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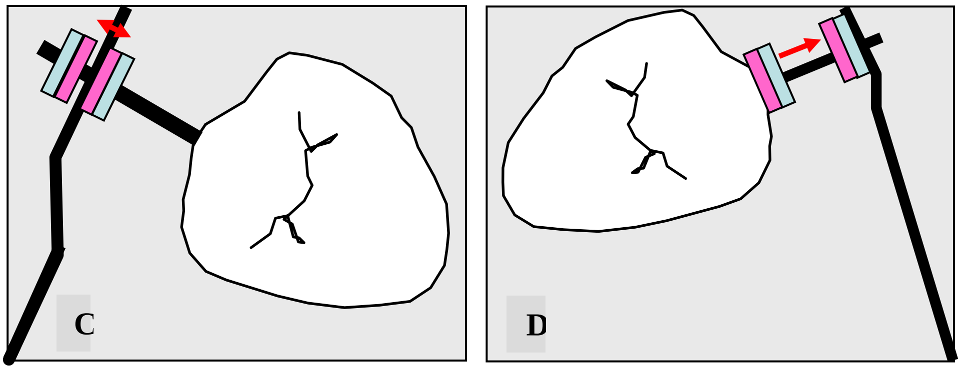


Descending **Ascending**

Figure 2

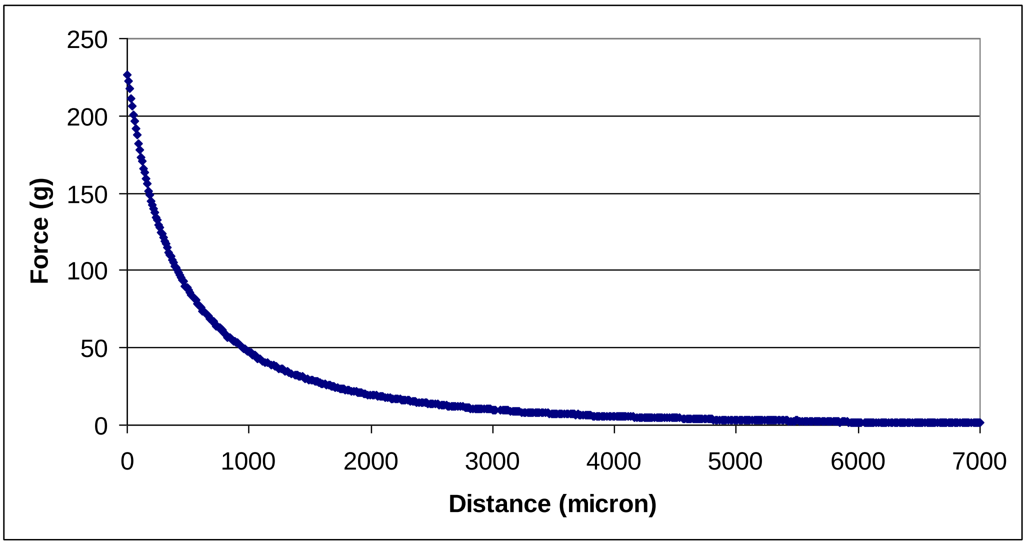


Figure 3

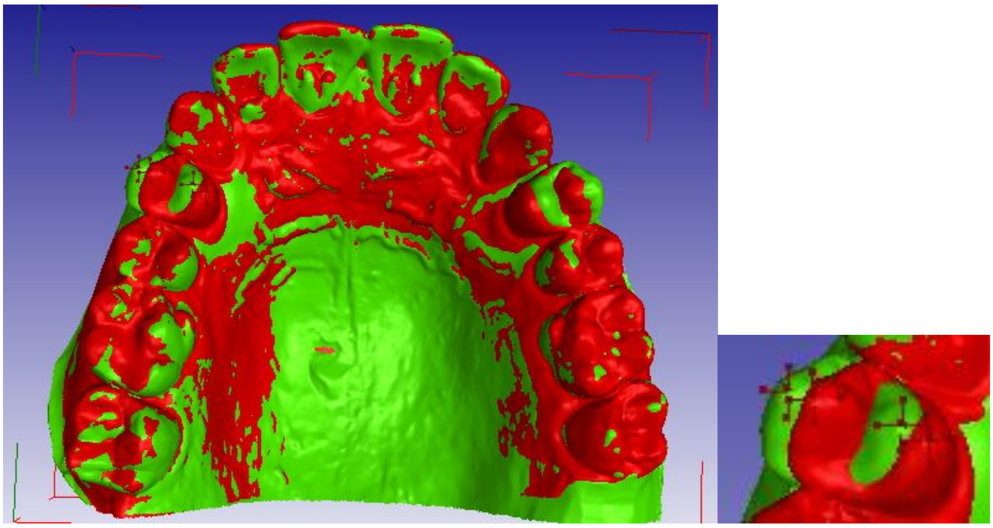


Figure 4

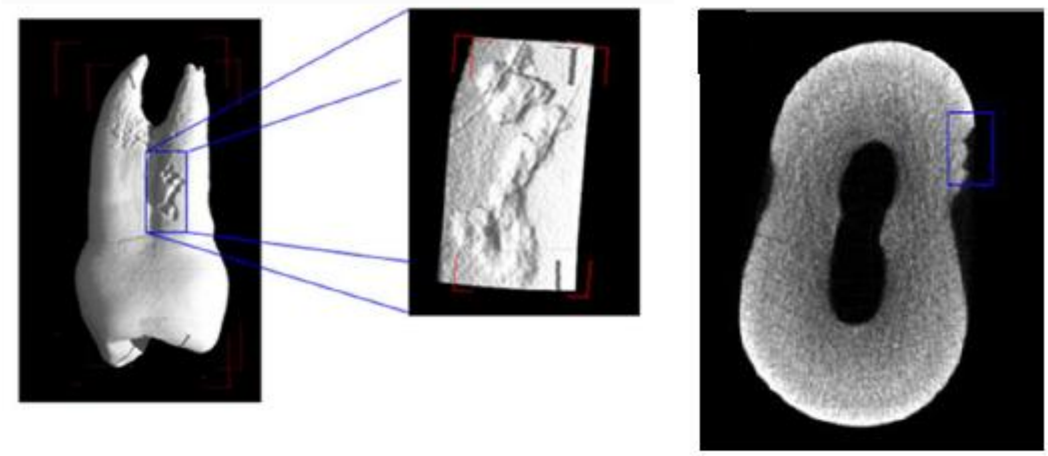


Figure 5

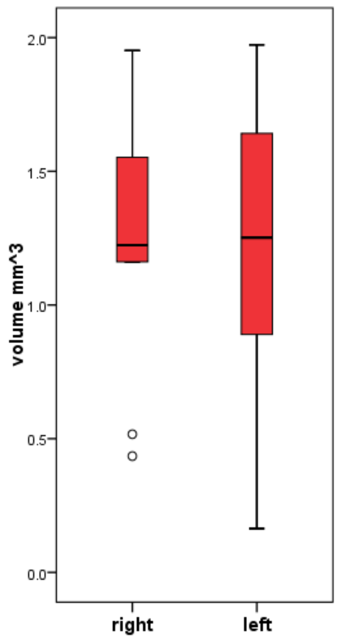


Figure 6. Right=Descending Force. Left=Ascending Force

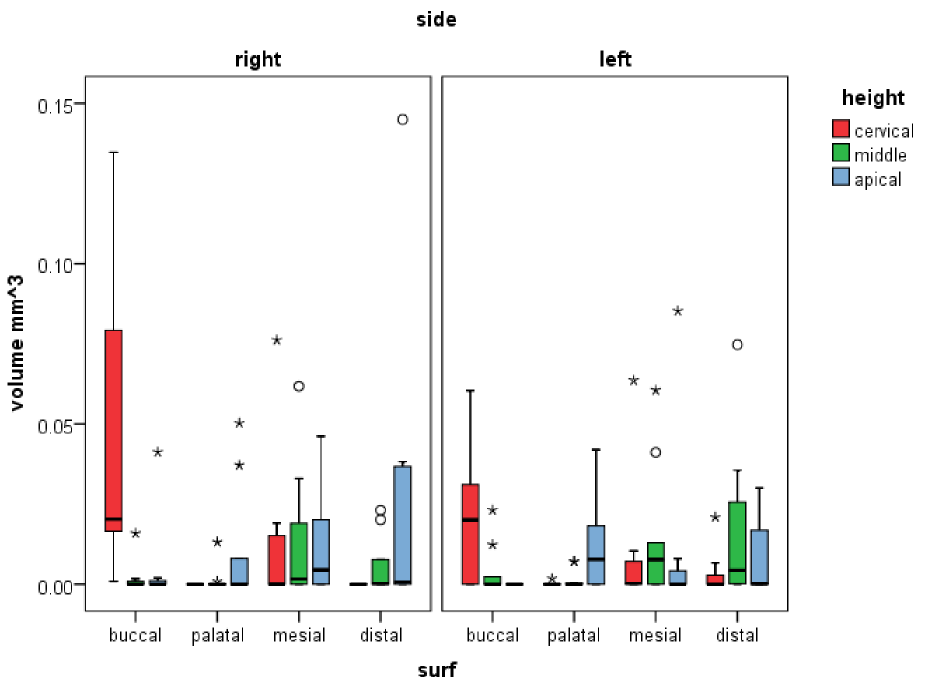


Figure 7 Right=Descending Force. Left=Ascending Force

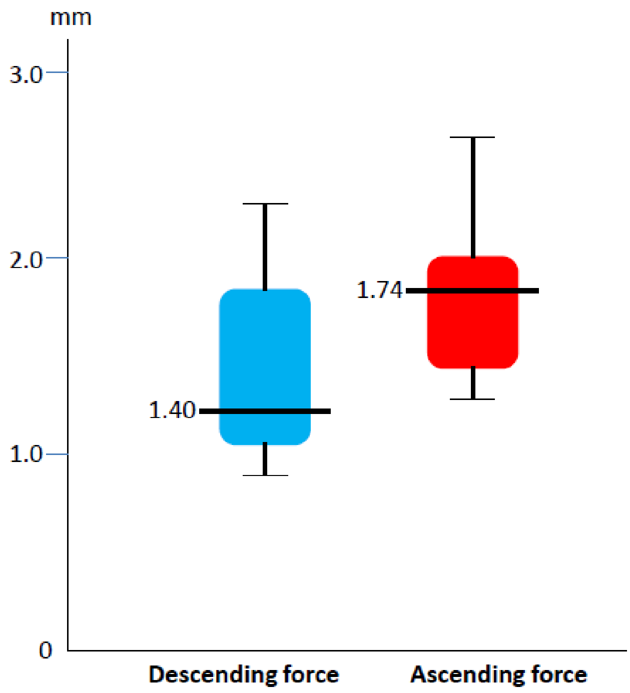


Figure 8

Force	Mean	Std. Error
Descending	1.248	0.120
Ascending	1.203	0.120

Table I

Height	**Descending** (±S.D.)	**Ascending** (±S.D.)	**Diff (Des-Asc)** (±S.D.)
Cervical	0.062 (±0.136)	0.031 (±0.064)	0.031 (±0.100)
Middle	0.022 (±0.048)	0.036 (±0.068)	-0.015 (± 0.058)
Apical	0.051 (±0.106)	0.030 (±0.065)	0.021 (± 0.086)

Table II

Surface	**Descending** (±S.D.)	**Ascending** (±S.D.)	**Diff (Des-Asc)** (±S.D.)
Buccal	0.057 (±0.110)	0.024 (±0.045)	0.034 (±0.078)
Palatal	0.012 (±0.034)	0.013 (±0.028)	-0.001 (±0.031)
Mesial	0.035 (±0.058)	0.032 (±0.065)	0.003 (±0.062)
Distal	0.031 (±0.084)	0.028 (±0.049)	0.002 (±0.067)

Table III

5.9. Figure and Table Captions

Figure 1. Appliance in situ. **A.** RHS buccal view. **B.** Maxillary occlusal view. **C.** LHS buccal view.

Figure 2. A. Diagrammatic presentation of appliance design. **B.** Magnet. **C.** Descending force. **D.** Ascending force.

Figure 3. Magnetic attachment Force-Distance graph.

Figure 4. 3D superimposing on palatal rugae to measure tooth movement.

Figure 5. Image of teeth with VGStudioMax software.

Figure 6. Box plot of the cube root volume of the resorption craters for the ascending and descending forces.

Figure 7. Box plot of the cube root volume of the resorption craters on regions of root surface.

Table I. Intraindividual differences of root resorption in (mm^3) between ascending and descending force.

Table II. Intraindividual differences of root resorption (mm^3) between different vertical regions.

Table III. Intraindividual differences of root resorption (mm^3) between different surface regions.

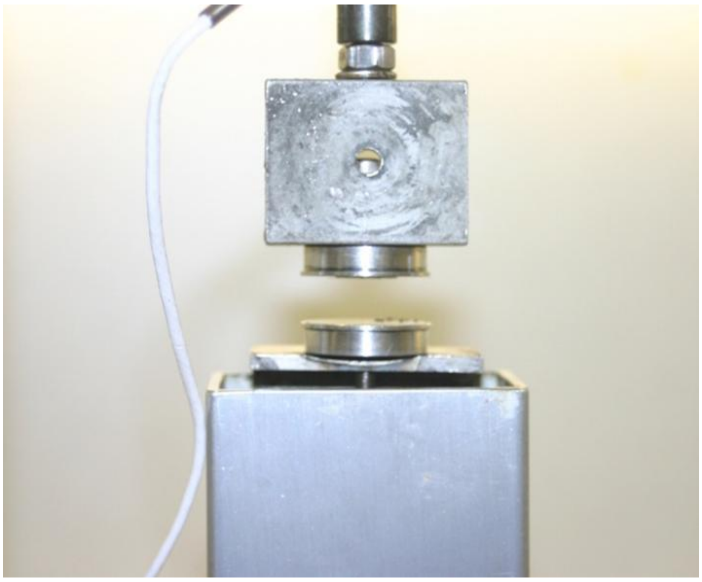
6. APPENDICES

6.1. Patient Selection Criteria

Patients were recruited according to strict selection criteria as described below:

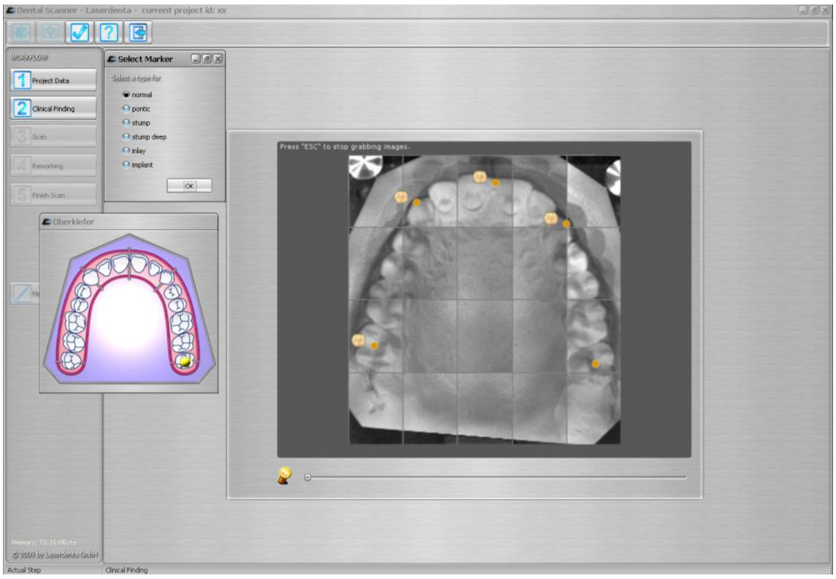
1. No previous reported or observed dental treatment to the teeth to be extracted,
2. No previous reported or observed trauma treatment to the teeth to be extracted,
3. No previous reported or observed orthodontic treatment involving the teeth to be extracted,
4. No past or present signs or symptoms of periodontal disease,
5. No past or present signs or symptoms of bruxism,
6. No significant medical history,
7. No physical abnormality concerning the anatomy of the craniofacial or dentoalveolar complex,
8. Completed apexification, and
9. Patient residence in particular region from birth without any migration.

6.2. Mach-1 universal testing machine

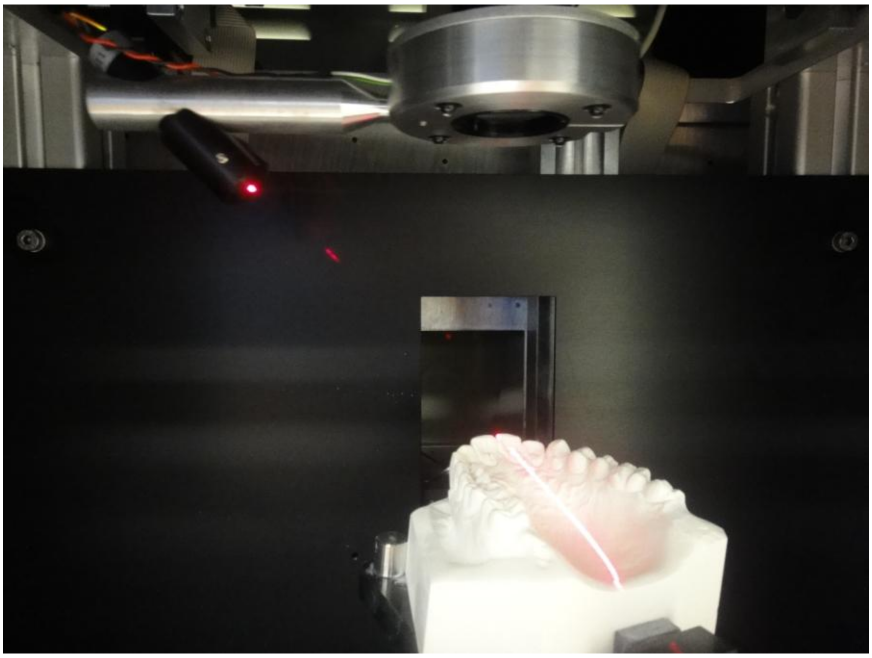


6.3. Laserdenta 3D surface scanner

Laser Dental 3D Laser Scanner System

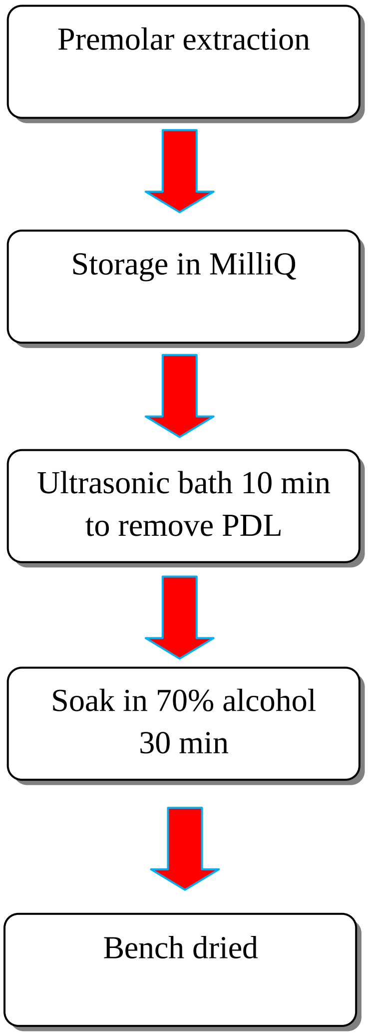


Open Scan Scanning Software



Scanning Procedure

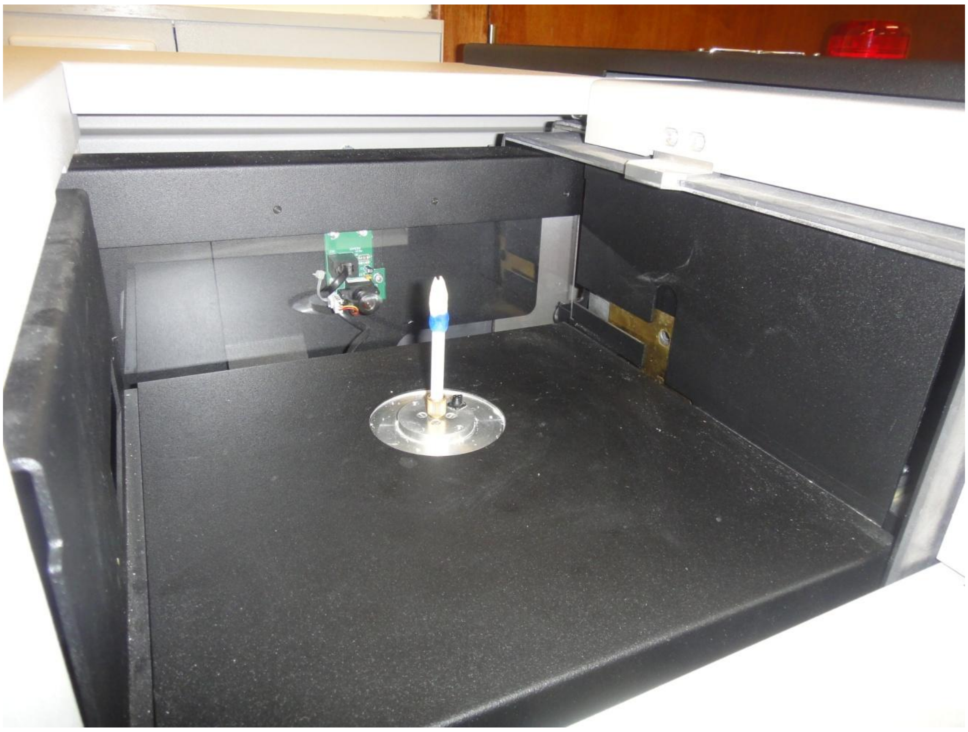
6.4. Specimen Storage and Preparation



6.5. Skyscan 1172 Micro CT (Skyscan, Aartselaar, Belgium)

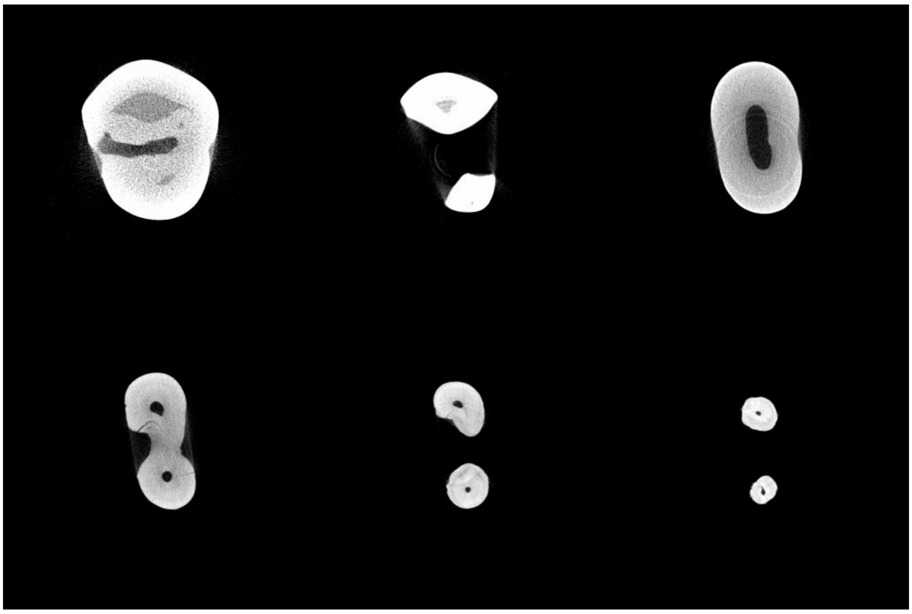
Skyscan 1172 desktop micro-CT system

Sample Mounting

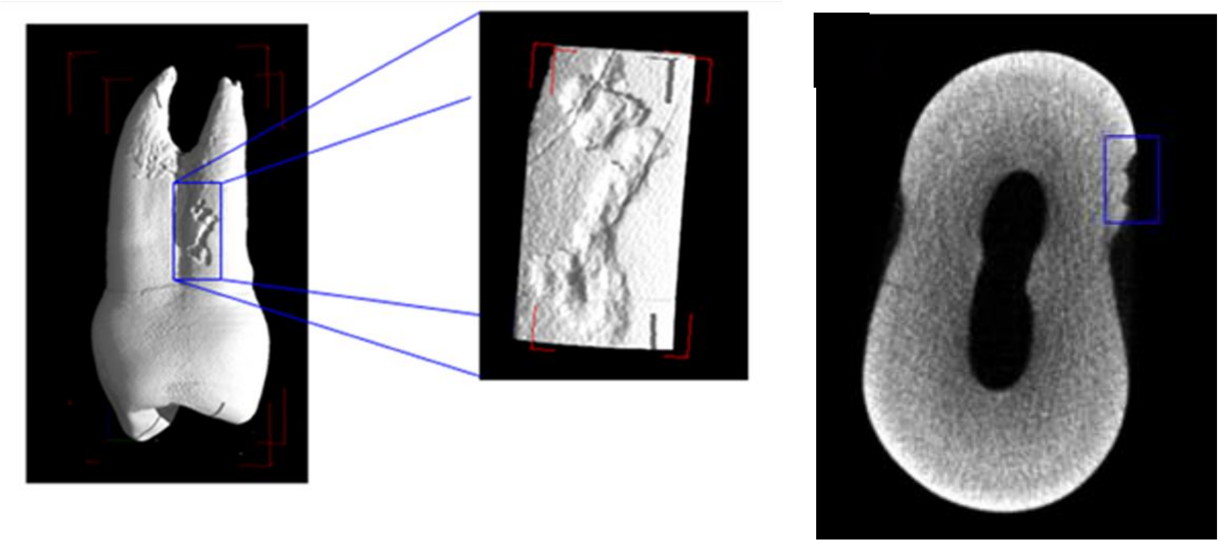


Raw Images from Micro-CT Scan

Reconstructed image series using NRecon Software



Visualization and Crater Isolation



Convex Hull 2D Algorithm

7. FUTURE DIRECTIONS

Orthodontic tooth movement involves bone remodelling and inflammatory process, therefore, OIIRR is an undesirable but unavoidable side effect of orthodontic treatment. Many studies have investigated the multitude of factors involved in this complex biological process. The magnitude of applied force has been a intensely investigated factor because of its effect on the stress distribution within the PDL, and the subsequent extent of hyalinization and associated frontal or underlying resorption. There are conflicting reports in the literature regarding the correlation of force magnitude and the amount of OIIRR and tooth movement.

Most studies examining the effect of force magnitude using either light or heavy force application. To our knowledge, apart from some animal studies, there are no reported studies investigating the effect of gradually changing force magnitude in human. Therefore, this study employed a novel approach using ascending and descending forces generated by a magnetic appliance.

Using sensitive and reliable investigative techniques, this study found no differences in the ascending and descending force application, both in terms of tooth movement and root resorption. In addition, the ascending and descending force had comparable RR to other conventional orthodontic force appliance. Although the sample size in this study was small, the statistical power analysis indicated that the sample investigated was large enough to detect a significant difference if there was one present.

To further investigate this topic, future studies can employ larger tooth movement range (such as space closure after extraction), longer treatment duration, and reduced heavy force levels.