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Abstract: Tissue regeneration is rapidly evolving to treat anomalies in the entire human body. The production of biodegradable, customizable scaffolds to achieve this clinical aim is dependent on the interdisciplinary collaboration among clinicians, bioengineers and materials scientists. While bone grafts and varying reconstructive procedures have been traditionally used for maxillofacial defects, the goal of this review is to provide insight on all materials involved in the progressing utilization of the tissue engineering approach to yield successful treatment outcomes for both hard and soft tissues. *In vitro* and *in vivo* studies that have demonstrated the restoration of bone and cartilage tissue with different scaffold material types, stem cells and growth factors show promise in regenerative treatment interventions for maxillofacial defects. The repair of the temporomandibular joint (TMJ) disc and mandibular bone were discussed extensively in the report, supported by evidence of regeneration of the same tissue types in different medical capacities. Furthermore, in addition to the thorough explanation of polymeric, ceramic, and composite scaffolds, this review includes the application of biodegradable metallic scaffolds for regeneration of hard tissue. The purpose of compiling all the relevant information in this review is to lay the foundation for future investigation in materials used in scaffold synthesis in the realm of oral and maxillofacial surgery.

Keywords: Materials, Maxillofacial, Tissue regeneration, Scaffold

1. Introduction

Extraoral craniofacial tissue engineering is a blossoming field that encompasses a wide variety of stimulating materials and bioactive agents incorporated into a scaffold to restore the anatomy and functionality of an injured or defected region.[1] Scaffolds are biocompatible, biodegradable three-dimensional constructs with a unique architecture that facilitate cell adhesion, migration, proliferation and differentiation.[2–36] Various biomaterials have been recently developed to accommodate the need for scaffold or implant fabrication and their surface modification aimed at regeneration and tissue engineering of different organs.[36–42] Craniofacial tissue engineering scaffolds and implants

can be composed of a specific material or a blend/composite of materials that correlate to the type of tissue being reconstructed, hard (bone) or soft (cartilage) tissue.[43–46] Important factors to take into consideration in the design and implantation of the scaffold include dimensions of the defect, cell density in the surrounding tissue, and available vasculature around the area of damage.[1] Signal-inducing growth factors and attached proteins can also mitigate mechanical property enhancement and cell-cell interaction within the complex.[47–49] While the scaffold is meant to facilitate the biochemical activity that gives rise to new tissue, its rate of degradation normally is equivalent to the rate of tissue formation.[48] The applicability of this division of regenerative medicine will be discussed in the two separate types of tissue application that routinely serve as surgical sites for oral and maxillofacial surgeons: cartilage and bone.

Approximately ten million people in the United States suffer from temporomandibular joint disorders (TMD).[50] Tissue engineering applied to the temporomandibular joint (TMJ) has been a part of scientific discussion and practice for three decades. Severe complications of the TMJ disc have led to discectomies, (which is the surgical procedure to remove the TMJ disc) but functional implants are being seriously considered as an alternative approach.[51] Displacement of the dysfunctional disc followed by the insertion of a cell source to manufacture neocartilage is the overall goal of current researchers in the field. Using a biocompatible scaffold seeded with cells and biological modulators can facilitate this process but the regeneration needs to be self-limiting and controlled so that ossification does not occur.[52] With current understanding of underlying causes of TMJ pathology and its instigation of myofacial pain in the patient leading to debilitating masticatory function, recent strides have been made to create a long-term resolution. The potential to induce regeneration of the TMJ disc depends on a variety of factors, such as scaffold design and material, supplementary cells, bioactive agents, biochemical compatibility between the scaffold and surrounding environment, and the ability of the host to accept the scaffold and facilitate a natural process that equates tissue formation with safe biodegradation of the three-dimensional construct. Two decades ago, several papers were published to demonstrate the capacity for a TMJ disc-specific regenerative mechanism.[53–55] In order to safely revitalize the natural environment of the disc, in addition to restoring its functional capabilities, the proper combination of biocompatible materials and bioactive agents needs to be employed, and a variety of these scaffold designs have been successfully tested *in vitro* and *in vivo*.[53,56] The soft tissue of cartilage can be regenerated using natural and synthetic polymers alike.[57,58] both classes of which will be further discussed in Section 3.

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Significant maxillofacial bone damage that requires tissue reconstruction may result from tumors, osteoradionecrosis, trauma, or congenital defects, and traditionally, these debilitating causes were addressed by bone grafting procedures.[59,60] Tissue engineering strategies to restore both the functional capabilities and morphology of lost bone tissue have made great strides in the last couple decades.[61,62] Tissue engineering can be employed for bone as well by providing permanent, biomimetic, replacement tissue systems. To reach this aim, scientists can utilize the tissue engineering model (Fig. 1). In this schematic, native tissue is first evaluated to generate design parameters.[63]

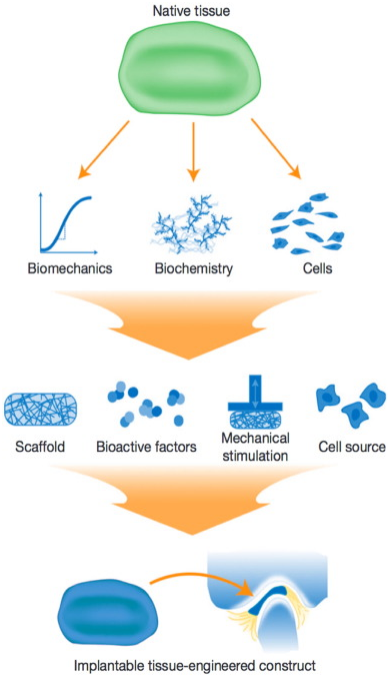

Fig. 1. Tissue engineering model applicable to TMJ tissues. The regenerative approach is initiated by the evaluation of biomechanical, biochemical, and cellular characteristics of the native tissue to generate design parameters for tissue engineering. Afterwards, cells are incorporated into scaffolds, bioactive agents, and mechanical stimuli to make a regenerated TMJ tissue that could be implanted *in vivo*.[63]

Two methods are notable in hard tissue engineering: *in situ* tissue engineering, which incorporates an acellular scaffold matrix into the site of tissue injury to attract local cells and osteoconductive mediators that will guide the process of regeneration, and *ex vivo* cell seeding on the scaffold, which would allow the cells to orchestrate the mechanism of bone formation.[59]

2. TMJ cartilage engineering

2.1. Materials for cartilage tissue engineering

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2.1.1. Collagen

Although the study of most natural polymers has been very limited in the regeneration of the cartilage disc, one stands out considerably among the rest in attempts to achieve total disc reconstruction: collagen.[64] Its ability to be broken down and used as a gel has led to its widespread use, especially because of the ease at which it can be injected as a delivery system suspension into the cartilage defect, although its use as a more rigid structure is more ideal because of the need for suitable porosity to allow for cell adhesion and proliferation throughout the scaffold.[65,66] Levingstone et al. similarly conducted an experiment to support the use of collagen in osteochondral defects, ultimately presenting evidence that collagen type 1 improved the mechanical properties of composite scaffolds for osteochondral defect repair.[67] Furthermore, Farrell et al. observed increased chondrogenic differentiation of mesenchymal stem cells in a rat model tested with a collagen-glycosaminoglycan scaffold.[68]

2.1.2. Gelatin

Gelatin, another natural polymer, is derived from the denaturation of collagen and is favorable because of its hydrophilicity and cross-linking ability.[69] Kuo and Wang[70] exhibited *in vitro* chondrogenic differentiation with a scaffold composed of gelatin and chitosan while Xia et al.[71] similarly yielded positive results with the same scaffold materials *in vivo*. Gelatin, although a recently developed material for the purpose of engineering cartilage tissue, is known to promote matrix-chondrocyte interaction, leading to the necessary cellular activity to regrow the native tissue.[72]

2.1.3. Hyaluronic acid (HAc)

Hyaluronic acid, as a polysaccharide derivative, is quite extensively used in the regeneration of cartilage. HAc hydrogels induce stem cell differentiation into chondrocytes and are powerful in cartilage matrix synthesis, as indicated by *in vitro* and *in vivo* studies alike.[73] Chung and Burdick, for example, demonstrated that HAc hydrogel scaffolds support chondrogenesis and gene expression that positively impacts protein synthesis required for cartilage regeneration.[74] Due to the fact that HAc is extremely abundant in synovial fluid and cartilaginous matrices, especially cartilage glycosaminoglycans (GAGs), its biocompatibility is well known to support a favorable cartilage microenvironment.[75] Yamane et al. reported that the addition of hyaluronic acid to hybrid scaffolds can also perpetuate an increase in mechanical properties of the scaffold to support cartilage tissue engineering.[76]

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2.1.4. Fibrin

Despite the fact that it has not been examined as vigorously as collagen, gelatin and hyaluronic acid, fibrin has additionally been researched as potential scaffold material for the culture of stem cells.[77] Willerth et al. has employed fibrin scaffolds for the culture of ES cell derived neural progenitor cells and decided the important soluble growth factor signs are expected to encourage the differentiation of such cells in neurons and oligodendrocytes.[78] Other authors have examined the behavior of mesenchymal stem cells seeded inside of fibrin clots and treated with growth factors for utilization in engineering bone.[79,80] Furthermore, fibrin-based scaffolds seeded with mesenchymal stem cells have likewise been employed for engineering cartilage.[81,82] Liu et al. has ascertained the suitability of fibrin scaffolds for encouraging vasculature formation from mouse ES cells.[83] They proposed an assortment of stem cell lines could be cultured inside of fibrin scaffolds for various tissue engineering applications.

2.1.5. Silk

The characteristics of silk make it appealing for engineering bone and ligament tissue and a broad study has been carried out utilizing 3D silk scaffolds in conjunction with mesenchymal stem cells for tissue regeneration applications.[77] Particularly, Meinel et al. have effectively created such strategies.[84] They have revealed that human mesenchymal stem cells combined with silk scaffolds can be employed to engineer bone. Also, this study ascertained that the stream conditions around the scaffold in addition to the characteristics of the scaffold impacted the rate of calcium deposition, which is a vital thought for bone tissue engineering. Another study investigated the use of silk scaffolds modified to contain RGD (arginine-glycine-aspartic acid) peptide sequences for the culture of human mesenchymal stem cells and cleared that the aforementioned scaffolds were suitable for supplanting bone due to slow scaffold degradation.[85] Other works have explored the role of pore size to determine its impact on the stem cell's behavior seeded inside silk scaffolds.[86,87]

2.1.6. Agarose

Agarose, which is extracted from red algae and seaweed, comprises of a galactose-based backbone and is usually employed as a medium for cell culture in the form of agar. One of the alluring characteristics of agarose is that its stiffness can be changed, taking into consideration tuning of the mechanical characteristics of the scaffold.[77] Agarose scaffolds have been evaluated in combination with stem cells in an assortment of tissue applications,

including cartilage, cardiac, and nervous tissue. A collection of studies has shown the appropriateness of agarose scaffolds for elevating stem cells to differentiate into chondrocytes.[88–90] The different stem cell types utilized in these works contained human mesenchymal stem cells, bovine mesenchymal stem cells and adipose-derived stem cells. Another research study affirmed that primate ES cells cultured inside of agarose scaffolds would form aggregates and differentiate into cardiomyocytes that would pound for up to one month.[91] Other works have revealed that both mouse and primate ES cells can differentiate into dopaminergic neurons when encapsulated inside of agarose microcapsules.[92,93] This technique could be utilized as a potential treatment for Parkinson's disease. In general, agarose scaffolds provide an adaptable platform for bone regeneration.

2.1.7. Polylactic acid (PLGA)

Poly-l-lactic-*co*-glycolic acid (PLGA) is a synthetic polymer that has great structural versatility and mechanical properties that can be manipulated—a feature that is indeed favorable in cartilage tissue regeneration. Uematsu et al. constructed a novel PLGA scaffold for the investigation of cartilage tissue regeneration and found that the polymer supported the infiltration and differentiation of MSCs *in vivo*.[94] PLGA is also approved by the FDA for medical applications, which has been undoubtedly rare for synthetic materials.[95] Conventional PLGA, nevertheless, does not match collagen's structural compatibility to the native cartilage tissue of the TMJ disc and only sub optimally induces the functionality of chondrocytes and other cells in the native tissue, according to Kay et al.[96] In an experiment conducted by Fan et al., they demonstrated that the addition of another polymer or two in order to produce a hybrid scaffold would ultimately sustain chondrogenesis and limit the degree of degeneration.[95]

2.1.8. Poly vinyl alcohol (PVA)

Poly vinyl alcohol (PVA) is a biodegradable and biocompatible polymer that has been implemented in the repair of cartilagenous defects because of its notable water content and hydrophilic behavior, in addition to its elastic and compressive properties.[97] Tadavarthy et al. demonstrated the biocompatibility of a PVA implant with the development of an Ivalon embolic material. The water content of PVA gels that measured 80%–90% by weight were implanted intramuscularly or subcutaneously into a rabbit for cartilage repair.[98] One of the first uses of PVA for articular cartilage replacement was reported by Bray and Merrill in the early 1970s.[99] There are many other studies that demonstrated the use of PVA in articular cartilage repair.[100–102] PVA hydrogel can be prepared with different polymer concentration and number of cycle tested to have tensile

strength in the cartilage range of 1–17 MPa[103] and Elastic modulus varying from 0.0012 and 0.85 MPa.[104] Furthermore, due to the fact that PVA has a low rate of degradation, its mechanical properties can be preserved, while still retaining a chondrogenic phenotype, as a scaffold for enough time until the neocartilage tissue is restored.[105]

2.2. Stem cells

Stem cell use in scaffold design and implantation is beneficial for TMJ disc regeneration as a result of multipotent differentiation into the fibrocartilage that composes the joint.[106] Extracting stem cells from the synovial capsule surrounding the joint holds promise for generating neocartilage. Bone marrow mesenchymal stem cells (BMSCs) also stimulated a higher rate of cell growth and division; its disadvantage is that the replaced tissue that the BMSCs generate is prone to endochondral ossification.[106] Moreover, adipose stem cells (ASCs) are advantageous in a low oxygen environment, which is the setting immediately following implantation of the scaffold. ASCs, upon differentiation, replicate the extracellular matrix environment and its components, including the various types of collagen.[107] The multilineage differentiation and abundant sources of adult mesenchymal stem cells make them the very suitable cell types in the regeneration of cartilage, among other tissues.[108]

The source of the stem cells can be utilized in the maxillofacial regeneration has been given as follow:

1. Bone marrow
2. Adipose tissue
3. Stem cells from oral and maxillofacial area[109]

2.2.1. Bone marrow

Bone marrow stem cells (BMSCs) can be reaped from sternum or iliac crest. It is made of both hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). The larger part of oro-maxillofacial structures is formed from mesenchymal cells. The upside of bone marrow is that it has a bigger volume of stem cells and can be differentiated into a wide assortment of cells. Isolation of BMSCs can be conducted only under general anesthesia with conceivable post-operative pain.[109]

2.2.2. Adipose tissue

These stem cells can be extracted from the lipectomy or liposuction aspirate. Adipose derived stem cells (ADSCs) include a group of pluripotent mesenchymal stem cells that display multilineage differentiation.[110] An advantage of adipose tissue is that it is easily obtainable and is plentiful in the human body.[109]

2.2.3. Stem cells from the oro-maxillofacial area

Stem cells from the oral and maxillofacial complex overwhelmingly contains mesenchymal stem cells. In this region, different types of dental stem cells were isolated and examined.[109,111] They contain:

(i)Dental Pulp Stem Cells (DPSCs)
DPSCs were the first tooth-derived stem cells characterized by Gronthos et al. in 2000, and they are mesenchymal inside dental pulp.[112] DPSCs are known to differentiate into various kinds of cells and tissues, such as osteoblasts, adipocyte-like cells, smooth muscle cells, neurons, dentin and a dentin-pulp-like complex.[113] They were additionally revealed to have chondrogenic potential *in vitro*. Their multipotency, proliferation rate, availability, and cell number have exhibited to be more noteworthy than those of BMSCs. Generally, DPSCs are more appropriate than BMSCs for mineralized tissue regeneration.[114]

(ii) Stem Cells from Human Exfoliated Deciduous Teeth (SHEDs)
SHEDs were identified to be cells of higher proliferation rate, with increased population doublings, immature multipotent clonogenic cells isolated from deciduous teeth that can differentiate into several cell types.[115] SHEDs are progenitor cells isolated from the pulp remnant of exfoliated deciduous teeth. It is worth mentioning that they display a higher proliferation rate with enhanced population doublings, immature multipotent clonogenic cells isolated from deciduous teeth that can differentiate into numerous cell types.[109,111,115] Osteoblasts, odontoblasts, adipocytes, and neural cells have been reported to differentiate from SHEDs.[113]

(iii)Periodontal Ligament Stem Cells (PDLSCs)
Although periodontal ligaments are known to be of neural crest cell origin, PDLSCs show stem cell characteristics similar to MSCs.[113] Additionally, PDLSCs residing in the perivascular wall have general characteristics in phenotype, cell morphology and differentiation potentials.[116] Immunomodulatory ability is another component that allows them to resemble BMSCs to some degree.[117] PDLSCs can differentiate into osteoblasts,

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cementoblasts, adipocytes, and chondrocytes, and they were described to form periodontal ligaments and cementum-like tissue *in vivo*.[111]

(iv)Stem Cells from Apical Papilla (SCAPs)
SCAPs are cells isolated from the root apex of a newly formed tooth, which is thought to be connected to root formation.[118] They introduce the features of MSCs and can differentiate into chondrocytes, adipocytes, osteoblasts and neurons under suitable states.[119]

(v)Dental Follicle Progenitor Cells (DFPCs)
DFPCs are stem cells obtained from dental follicles encompassing a tooth germ in early tooth formation phases.[120] The dental follicle is an ectomesenchymal cell condensation and harbors heterogeneous population of cells, including those within the periodontium. They are similarly known to differentiate into osteoblasts, chondrocytes, adipocytes and neuronal cells.[113,121]

Since DPSCs are the most concentrated on in the literature, we will focus mostly on the utilization of DPSCs in this section.

In a clinical research study, biocomplexes fabricated from DPSCs and collagen sponges were employed in human mandible repair and showed excellent results.[111] In conjunction with other scaffolds, DPSCs have been cleared to have osteogenic differentiation ability.[122–124] The topography of the scaffolds was described to assume an important role in clinical regeneration.[125]

With regard to alveolar bone defects, Liu et al. proclaimed that DPSCs expressing bone morphogenic protein 2 (BMP-2) experience prior mineralization and produce a more noteworthy amount of bone in a rabbit model.[126] Preceding this perception, proof with respect to the impact of BMP-2 on the osteoinducibility of DPSCs was reported by several authors.[127–129] Platelet rich plasma has also been examined in the same context.[62,63,111,130,131]

The role of DPSCs in bone regeneration around dental implants was, as of late, studied,[131] and a comparable study was done with BMSCs; periosteal cells displayed that DPSCs describe the most astounding osteogenic potential as a source for tissue-engineered bone around titanium implants.[132] Furthermore, a late report recommended that immobilization of DPSCs in alginate hydrogels results in increased osteogenic potential contrasted with control cells cultured in routine stem cell media.[133]

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Osseous regeneration employing PDLSCs has been evaluated by multiple studies. For example, Chadipiralla et al. thought about the *in vitro* proliferation and calcium deposition of PDLSCs with SHEDs through retinoic acid treatment with insulin and demonstrated that PDLSCs display unrivaled characteristics.[134]

Osteogenic differentiation of DPSCs has happened in conjunction with other material substrates.[135] In the Mangano et al. study, the DPSCs were cultured *in vitro* on different titanium surfaces and differentiated into osteoblasts, leading to synthesized bone on laser-sintered surfaces.[124] Lately, Akkouch et al. found that DPSCs had been pre-differentiated into osteoblast-like cells and seeded onto collagen–hydroxyapatite–poly(l-lactide-*co*-ε-caprolactone) composite scaffolds.[122] They concluded that the composite scaffold encourages adhesion, proliferation and differentiation of the osteoblast-like cells, with ECM mineralization happening all throughout the scaffold. Kanafi et al. examined the possibility of immobilizing DPSC s within alginate microspheres and evaluated the *in vitro* osteogenic differentiation potential. Increased mineralization, protein secretion and an upregulated osteo-related gene profile came about because of immobilization and, curiously, immobilization activated osteogenic differentiation of DPSCs without the utilization of induction variables in the media.[133]

2.3. Growth factors

Growth factors are highly potent and serve as a popular bioactive agent in scaffold delivery. Basic fibroblast growth factor (bFGF) is extremely useful for cell proliferation and production of collagen. GAG synthesis is significantly stimulated by bFGF and platelet derived growth factor (PDGF) as well.[136] Delivering a combination of two growth factors produces a more reconstructive effect than a single growth factor alone. Together, their cooperation contributes to the repair of the disc. Moreover, IGF-1 and bFGF synergistically aid in the biosynthesis of disc cells.[137] The growth factors induce cell proliferation but fail to synthesize the matrix of the TMJ disc.[107] The purpose of using growth factors essentially is to upregulate, at a biochemical level, the proliferation of fibroblasts and chondrocytes that will, in turn, give rise to the regeneration of hyaline cartilage, extracellular matrix components, glycosaminoglycans, and other tissues that compose and surround the temporomandibular joint cartilage.[138] It is well supported in the literature that IGF-1 is dominant in its effect to repair cartilage by stimulating chondrogenesis *in vitro* and *in vivo*, while also increasing the GAG fraction of the construct.[139,140] Additionally, Blunk et al. specified that although PDGF is known to have an anabolic effect in cartilage protein synthesis and expression, more notably in cartilage explants, their experimental findings did not conclude that it was consistently favorable for cartilage tissue regeneration due to

its role in decreasing the scaffold growth rate. They lastly demonstrated that the application of TGF-β also induced ECM deposition and an increase in the total fraction of collagen in the cartilage engineering construct.[141]

Addition of growth factors into scaffolds might be refined in various routes, each of which presents distinctive characteristics. Immersion of a scaffold in growth factor-containing solution results in a loose connection with the structural material, and, in this manner, it encourages a snappy release of the craved stimulatory molecules. Alternately, growth factors might be added to and even covalently connected to the scaffold microstructure for augmented release. Cells adjusted to express and secrete osteoinductive growth factors may likewise be seeded in the scaffold, accomplishing a comparable impact.[142,143] The fundamental cell adjustments ordinarily include gene therapy accomplished either by viral or nonviral transduction. Viral transduction is the best method of gene transfer and is commonly conducted utilizing retroviruses, adenoviruses, or adeno-associated viruses.[144,145] Gene transfer can also be carried out through direct uptake of gene-including plasmids from solution or as a conjugate with a nucleus-bound biomolecule.[142,145]

Issues with growth factor-loaded scaffolds are mostly associated with inconsistent release profiles. The release of growth factor is regularly managed by passive diffusion or degradation rate and does not fittingly parallel the rate of bone regeneration and healing.[142,143] It has been demonstrated that covalent linkage of the growth factor to the scaffold may be sluggish and boost its release profile to more firmly surmised cellular requests.[146] For instance, covalently linked VEGF in a fibrin scaffold results in a more firmly controlled release and, in this way, a more sorted out vascularization in contrast with the scaffold with unlinked VEGF.[147] One peril inborn in covalently liked growth factors is changing mechanical, osteoconductive, or other characteristics of the scaffold material. However, it has been employed in animal models to effectively repair mandibular, zygomatic, and calvarial bone defects.[142,148]

In spite of such auspicious clinical accomplishments of growth factors for tissue regeneration, debates still hound their clinical employment for tissue regeneration of the oral and maxillofacial region. The greatest debate deals with the oncogenic capability of growth factors. Numerous tumors containing malignancies in the oral and maxillofacial region have, as of now, been demonstrated to over-express the previously stated growth factors such as TGF-β, BMPs, *etc.*, which are undoubtedly valuable for tissue regeneration when expressed in sufficient quantity. For the clinical trial of growth factors, supraphysiological doses are needed for compelling tissue regeneration in addition to

enhancing the demise of tumor development. Lamentably, the optimum concentration and suitable planning for administering growth factors are not completely settled, which might be essential for fruitful clinical results without tumorigenic side effects. Biologically, growth factors more often react to each other in an exceptionally sensitive and modern way, trading criticisms from the responding cells and tissues. Thus, growth factors frequently have biphasic features contingent upon the condition of the tissue. For instance, startling deferred tissue regeneration might occur because of the upregulation of a growth factor inhibitor when an exogenous growth factor is in excess for the tissue condition. By stabilizing the appropriate dose of growth factors and the timing of their release, more studies are expected to comprehend the exact mechanisms of the falls of growth factors when the defected tissue is repaired. Furthermore, a solitary dose of exogenous protein is surely understood not to affect a biological response satisfactorily in traded off tissue conditions1,2. As examined by Ripamonti et al., there is much to examine regarding growth-signaling molecules in tissue, including contrasts among animal and human models. Along these lines, blind confidence in utilizing growth factors for target tissue regeneration ought to be dodged, and more meticulous contemplations ought to consequently be supported before utilizing growth factors.

3. Mandible bone regeneration

3.1. Materials for mandible regeneration

3.1.1. Bioceramics

3.1.1.1. Calcium phosphates

Calcium phosphates are main components for dental, craniofacial and orthopedic treatments because of their similarity to bone composition, which can encourage the production of a useful functional interface.[149,150] One category of calcium phosphates, known as calcium phosphate cements, including dicalcium phosphate anhydrous and tetracalcium phosphate, was indicated to be a suitable choice for dental and craniofacial applications.[149,151] Calcium phosphate cement implants would be dependent on initial loading by temporary dentures and need to be resistant to flexure for periodontal bone treatments, mandibular and maxillary ridge augmentation. Furthermore, significant regeneration of the mandible and maxilla after trauma would benefit from calcium phosphate cement with optimal mechanical properties and rapid bioactivity, owing to cultured stem cells.[152] Hydroxyapatite (HA), a common calcium phosphate, has been utilized for maxillofacial tissue engineering.[153] In a research study, HA-based (n-

HA/polyamide (PA)) scaffolds that had been produced using CAD/CAM models based on CT data were implanted into a mandibular condyle defect. The patients eventually obtained a jaw contour and appearance with the suitable temporomandibular joint function.[154] In another report, HA porous scaffolds with 30 MPa compressive strength were implanted into mandibular defects, and these scaffolds were produced with two channel geometries, including orthogonal and radial shapes, with the channel size of 444 and 366 mm and porosities of 44% and 38%, respectively (Fig. 2).[155] As it can be observed in Fig. 3, four defect sites were produced in each hemi-mandible. Three defects on each side were filled with HA scaffolds, and the last one was left as the control group. The results of this study indicated that although normal regeneration of bone tissue was found at 5 and 9 weeks in both designs, at 9 weeks, the average bone ingrowth increased to 45,721 and 23,728% in the orthogonal and radial designs, respectively confirming that it is possible to control the morphology of the regenerated bone tissue inside HA scaffolds through the design.[155]

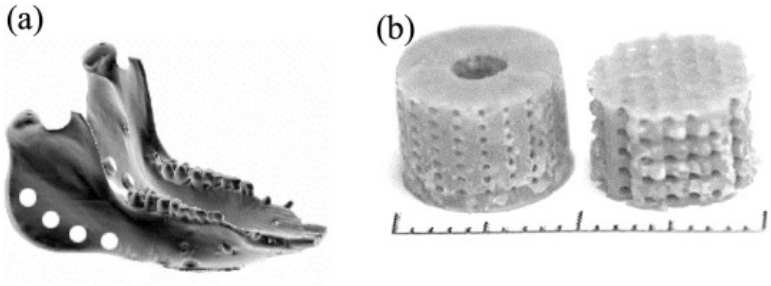

Fig. 2. (a) The locations of the defects in inferior posterior border of minipig mandible for implantation of sintered (b) radial (left) and orthogonal (right) design of HA scaffolds. The scale bar is 2 cm.[155]

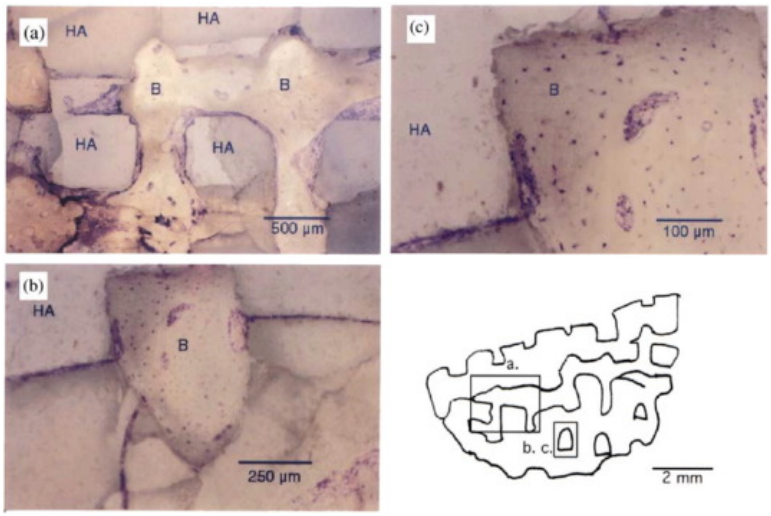

Fig. 3. (a) Bone regeneration through the pores of orthogonal design after 9 weeks. (b) Cross section of HA scaffold in low (b) and high (c) magnifications showing the regenerated bone structure. The location of tissue sections for imaging has been shown in right diagram.[155]

In the control group (Fig. 4), although new bone formation increased gradually, woven bone and fibrous tissue were more frequently observed. Considering the obtained results, the authors concluded that porous nHA/PA composite promoted bone formation over the extension of the defect and offers interesting potential for maxillofacial reconstructive procedures in load-free areas.[156]

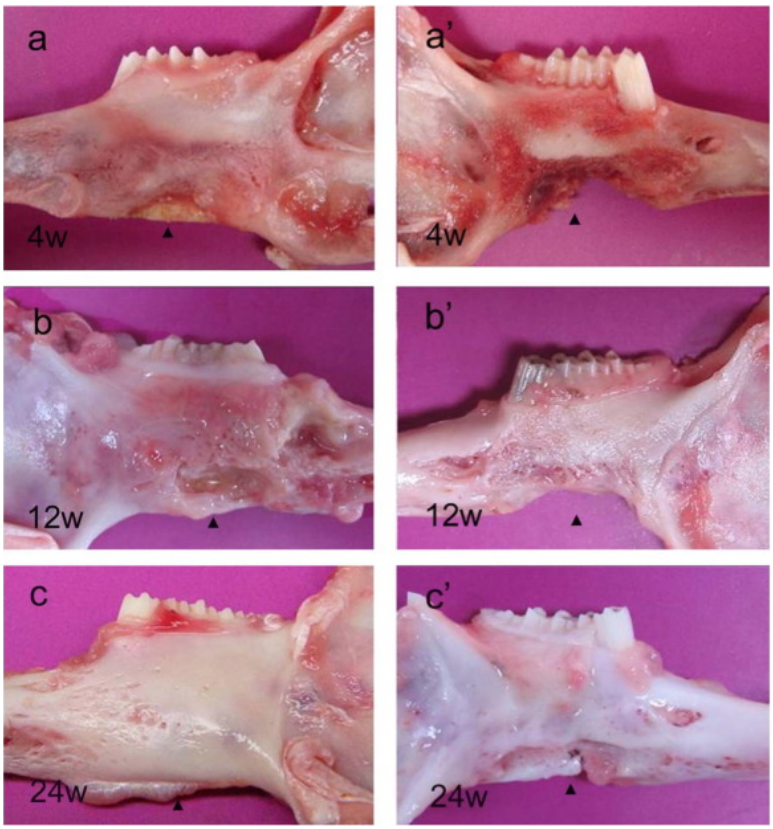

Fig. 4. Surgery images from nHA/PA implants after 4, 12 and 24 weeks. Left side includes the samples and right side is a blank control. Arrows show the defect area.[156]

3.1.1.2. Bioactive glass

Bioactive glasses (BaG) possess exceptional bioactivity, ability to deliver cells, and adjustable degradability.[157] The aforementioned properties made BaG a potential scaffold material for tissue engineering.[157–160] BaG is reported to be able to induce more bone synthesis compared to other bioactive ceramics. *In vitro* research studies show that their osteogenic behavior is mainly owing to their dissolution products stimulating osteoprogenitor cells at the genetic level. The osteoconductivity mechanism is due to the deposition of a hydroxycarbonate apatite (HCA) layer on the surface of the BaG.[161] Several classes of BaG have been recently introduced, including the conventional silicates, such as

BaG 45S5, phosphate-based glasses, and borate-based glasses. The BaG 45S5 has been employed in over a million patients to treat bone defects in the jaw and different orthopedic sites.[157] Its main marketing accomplishment is an active repair agent in toothpaste, under the name NovaMin. Clinical trials indicate that the dentifrice can mineralize tiny holes in dentine, reducing tooth sensitivity. BaG 45S5 has proven to be very stable into tooth extraction sites for treatment the tooth roots and providing a stable ridge for dentures. A 5-year research study indicated improvements over HA tooth root implants.[157] Since dentists, surgeons and engineers desire a material that can fill in defects easily, particles have a preferable morphology for this purpose. The first particulate BaG 45S5 product with a particle size range of 90–710 μm was PerioGlas as a synthetic bone graft for the repair of defects in the jaw that result from periodontal disease. It can be utilized to stimulate hard tissue regeneration in the jaw, so the bone quality becomes enough for anchoring titanium implants. PerioGlas is now sold in over 35 countries. For infra-bony defects between the roots of molars, clinical examinations confirmed that its regenerative behavior was increased with laser therapy after surgical treatment.[162] The product has also been utilized with polymeric membranes for guided tissue regeneration.[163]

The BaG research program in Finland caused the commercialization of S53P4 particulates known as BonAlive, which has received European approval to serve as a bone graft substitute in 2006. While the mandible has been basically composed of dense cortical bone that can be grafted, the maxilla consists of porous cancellous bone that resorbs quickly in periodontitis and is thus harder to graft. Treatment is typically maxillary sinus floor lifting, whereas bone grows partly into the sinus defect. In comparison to an autograft, a combination of BaG particles with autologous bone allowed the implantation of titanium dental implants in the maxilla and presented faster bone treatment with thicker trabeculae.[164] Clinical trials indicate that the BaG 45S5 particles adhere to the dentine, relieving the pain for longer periods.[165] Although, BaG particles have been popular in bone defect treatments, new components are necessary for porous scaffold production and regulatory approval.[157]

3.1.2. Polymers

Natural scaffolds including chitosan, collagen, and hyaluronic acid have proven to be bioactive and, thus, appropriate for bone creation both *in vitro* and *in vivo*.[166] However, a main drawback is the lack of mechanical stability. Synthetic polymers for example poly lactic acid (PLA), poly glycolic acid (PGA), polylactic-*co*-glycolic acid (PLGA), poly methyl methacrylate (PMMA) and polycaprolactone (PCL) have been introduced as alternatives

with structural integrity. The aforementioned polymers display potential for osteoblastic differentiation and bone tissue development and are normally employed for oral and maxillofacial tissue applications.[166]

The first generation of barrier function materials was non-resorbable, with expanded polytetrafluorothylene (ePTFE) membranes becoming the most commonly used.[167–169]

Since 1982, when guided bone regeneration (GBR) method was first established, the e-PTFE membrane has been considered a gold standard for barrier function materials.[170,171] Certainly, this non-resorbable material has all the characteristics for the GBR method, such as biocompatibility, covering the defect and coagulum stabilization;[172] however, e-PTFE membranes have certain cutoff points, such as the need of a second surgical operation to evacuate them and the likelihood of bacteria infection.[173–176] Actually, ePTFE-membrane exposure to the oral cavity dependably brought about a failure of the treatment.

Seibert and Nymann employed e-PTFE non-resorbable membranes to enhance the alveolar crest; after 55–90 days, the bone completely topped off the defect.[177] Urban et al. utilized e-PTFE membranes associated with autogenous grafts for implant insertions and demonstrated that implants placed were osseointegrated, and along these lines, the vertical GBR method is both protected and unsurprising.[171]

Other than avoiding a second surgery, resorbable membranes are likewise invaluable due to the boost in soft tissue healing and a lower bacterial contamination risk because of reduced exposure from the degrading membrane.[177] Notwithstanding the necessities expressed beforehand, there are further properties that these barrier membranes must satisfy: biocompatible degradation products that don't meddle with bone regeneration, a suitable degradation profile to synchronize with new tissue growth, and adequate mechanical and physical characteristics to carry out the barrier function and permit *in vivo* utilization.[167,178]

Among the widely recognized bioresorbable membranes are synthetic polyesters (poly(lactic acid), poly(glycolic acid), and poly(caprolactone) and their copolymers)[167,179–182] and tissue-derived collagen[167,183–187] Polyester membranes show biocompatibility and have a high level of customization, with degradation rates and mechanical characteristics that can be balanced in view of polymer composition and concentration.[167,188,189] As a natural component of the extracellular matrix, collagen is biocompatible and cell adhesive.

Despite the fact that collagen is not innately mechanically stable, it can be changed *via* different means of crosslinking.[178] Poly(ethylene glycol) (PEG) is otherwise a biodegradable and biocompatible polymer. Since numerous oral and maxillofacial defects are uniquely shaped, an injectable material is alluring, such as a PEG-based *in situ* forming gel for GBR that exhibited adequacy in a clinical trial.[190–192] Poly-DTE-carbonate has displayed promising characteristics, such as low immunological response and high ability to incite bone regeneration.[170,192]

A number of works on resorbable membranes have been performed to examine the conditions associated with various experimental and human models. Specifically, Gottlow (1984) demonstrated that a biological space impelled right bone regeneration, while without this space the membrane caved in and thus traded off bone regeneration.[170,193]

Hyder et al. and Kodama et al. stated that the inflammatory infiltrate incited by synthetic membranes was lower than heterologous animal membranes.[194,195] Robert and Frank displayed that, changing the polymer concentration, the membranes persist for about 4 months.[196] Laurel et al. cleared a period of resorption between 6 and 12 months, but the hydrolyses of the membrane led to little inflammation.[197]

A final note encompassing polymeric scaffolds for bone tissue engineering is that single polymer-derived scaffolds are not significantly applicable to maxillofacial bone tissue regeneration strategies; therefore, this paper will more heavily focus on the diverse composites used to make a substantial impact in hard tissue growth.

3.1.3. Polymer Matrix Composites (PMC)

Polymer matrix composite materials have been extensively used for the regeneration of bone. A primary reason for combining polymers and ceramics in hybrid composites is to integrate the advantages of each class of materials into one, making an optimal blend with suitable mechanical strength, osteoconductivity and biodegradability for effective bone tissue formation.[198–204] One such example is PLLA / HA, and it has been utilized successfully as an osteochondral construct for mandible bone engineering by the porcine chondrocytes delivery in the polymer layer and fibroblasts transduced with adenovirus driving the expression of bone morphogenetic proteins.[205] In a pilot *in vivo* study, eight dogs were used for a model of the mandibular condyle that had been produced by rapid prototyping of PGA/PLA scaffold that was then seeded with bone mesenchymal stem cells. While research studies have explored the appropriateness of different kinds of materials in making the CAD/CAM scaffolds, histological evaluations focusing on bone

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mesenchymal stem cells seeding in scaffolds have confirmed that PGA/PLA is one of the best available choices for the new bone regeneration.[206] Xu et al.,[206] have introduced a technique for production of PGA/PLA mandibular condyle porous scaffolds for bone regeneration that confirms outstanding morphological modification and accuracy. Moreover, synthetic biodegradable polymers such as PGA/PLA can be freely adjusted to the shape of a defect. Zhou et al.[207] indicated that physiological healing of articular cartilage defects and the corresponding subchondral bone is possible *via* autologous bone mesenchymal stem cells and PGA/PLA polymers. This study confirms that PGA/PLA has appropriate cytocompatibility due to the bone mesenchymal stem cells dispersed in PGA/PLA scaffold.[206]

Post-operative analysis is common in most circumstances of *in vivo* testing of scaffold implantation and subsequent hard tissue engineering because it is necessary to carry out histological evaluation to evaluate both the effectiveness of the scaffold in tissue repair and to monitor the site for any adverse reactions from the host in response to the scaffold. In another *in vivo* research study, a 2 cm incision was created in the lower edge of the mandible body of adult New Zealand white rabbits and was filled with porous nano-hydroxyapatite/polyamide composite (nHA/PA). After the surgery, no necrosis, inflammation or postoperative complication was seen in any animal, and the bone defects were healing well. At 1 month, macroscopic inspections indicated that the scaffold was stable in the defects and the amount of callus creation was significant enough that nearly 70% of the implant surface was covered. According to the results of macroscopic, radiographic, histological and histomorphometric examinations that were carried out up to 6 months postoperatively, the defects were entirely occupied by neo-bone with density similar to the host bone.[156]

Chitosan has been a potent material in the rampant use of wound-healing agents in maxillofacial and periodontal regeneration as well. Its osteoinductivity was supported by confirmative mineralization of hard tissue following the extraction of third molars.[208] Chemical mediators, in fact, are so effectively enhanced by the addition of chitosan that the number of osteogenic colonies drastically increases in patients with chronic bone defects, such as periodontitis.[209] Zhou et al. prepared two types of scaffolds composed of different PMCs by way of homogenization and radiation crosslinking.[210] Results showed that both scaffolds demonstrated remarkable biocompatibility and biodegradation following *in vivo* implantation in the mandible of beadle dogs, and osteogenesis occurred at the outer edges of the scaffolds initially before moving inward toward the center, with gelatin/CM-chitosan/β-TCP quantifiably containing a higher volumetric density than gelatin/CM-chitosan composite.[211]

3.1.4. Ceramic Matrix Composites (CMC)

While PMCs are more flexible and more easily maneuverable than ceramic matrix composites for filling the shape of an irregular bone defect, CMCs have a distinct advantage in increasing the mechanical strength of the construct to withstand load-bearing applications, especially the compression of the jaw.[212] However, it is more difficult to implant the scaffold because of its brittle nature; therefore, fitting the scaffold into the shape of the defect is a challenge for surgeons and could result in increased time of surgery as well as surrounding tissue damage.[213,214] Xu et al., furthermore, demonstrated that while CMC scaffolds are durable and strong enough to withstand immense compressive force, the addition of a polymer, such as chitosan, can induce macropore formation for bone ingrowth and can also lead to a synergistic hardening and an overall superior fracture resistance.[215]

A strong example of inorganic CMC scaffolds include cements composed of calcium phosphate (CaP's) and typically either hydroxyapatite, β-tricalcium phosphate (β-TCP), or bioactive glass.[216] CaP's, in particular, have demonstrated that doping scaffolds with other inorganic materials not only stabilize certain factors, such as mechanical strength and dissolution rates.[217–219] Similarly, the addition of oxides to β-TCP scaffolds may result in 150% increase in compressive strength and approximately 90% rise in cell viability.[217] Furthermore, Biphasic hydroxyapatite (HA)/TCP was investigated by Cavagna et al. in 109 orthopedic spinal fusion patients, showing the compound's promise in load-bearing bone tissue engineering applications.[220] Ashuri et al. also experimentally demonstrated that a novel HA/bioactive glass scaffold exhibited optimal mechanical strength with 20 wt.% bioactive glass, but it eventually decreased over time following immersion in simulated body fluid (SBF).[5] Although CMC scaffolds have their own distinct advantages applicable to craniomaxillofacial regeneration, as noted above, the literature appears to support the claim that PMCs are more widely applicable to these applications in medicine and provide scientists and clinicians with a greater sense of optimism moving forward in the field.

3.1.5. Metals

Biodegradable metals (BMs) are anticipated to corrode gradually *in vivo*, with a suitable host reaction evoked by released corrosion products, then wholly break down after satisfying the purpose of assisting with tissue recuperation without implant deposits [221]. Among BM frameworks, Mg-based BMs, which now have several applications reported in past clinical trial results, are viewed as effective material types for potential application in treating maxillofacial bone defects.[22,221]

Mg is mostly applied in bone tissue regeneration, it is an important element in the human body, and its presence is useful to bone growth and strength.[222–227] It is a cofactor for several enzymes and serves as a stabilizer of DNA and RNA structures.[228] Additionally, Mg is that the fourth most copious ion in the human body, further indicating its biocompatibility.[229,230] In extracellular liquid, the level of Mg reaches somewhere around 0.7 and 1.05 mmol/L, and its homeostasis is kept up by the digestive tract and kidneys.[222,223] The frequency of hyper-Mg is uncommon because of the effective excretion of the element in urine.[222,229]

Mg is osteoconductive and a bone growth stimulator material, as proposed by numerous studies. A remarkable increment of bone deposition has been seen in Mg-based implants compared to some polymeric scaffolds, such as PLA.[231–240] The erosion layer around Mg inserts has been discovered to contain calcium phosphates, which seemingly makes it in direct contact with the encompassing bone.[231] Xu et al. demonstrated new bone formation around Mg-Mn-Zn implants in their *in vivo* application in rats.[241] Witte et al. revealed that three months after the operation, open porous Mg scaffolds inserted in rabbits were mostly degraded, foreign body giant cells phagocytizing the remaining corrosion products were rarely found, and no osteolytic changes were discovered around the insertion site.[242] It has been demonstrated that porous Mg has better degradation characteristics, including lower pH change, slower hydrogen development, and slower decrement of compressive strength in simulated body fluid (SBF) soaking tests.[243] Zreiqat et al. revealed an enhancing bone cell adhesion on Mg-doped alumina, as communicated by an increased level of a5b1 integrin receptor and collagen extracellular matrix protein.[244] Two studies using Mg-doped apatites or collagen materials displayed strong biocompatibility on bone cell adhesion and tissue growth.[245,246]

Mg and its alloys are extremely lightweight metals, having density going from 1.74 to 2.0 g/cm^3, which is less than that of Ti alloys (4.4–4.5 g/cm^3) and is near that of native bone (1.8–2.1 g/cm^3).[224] They have an extensive variety of elongation and tensile strength properties from 3% to 21.8% and from 86.8 to 280 MPa, respectively. Mg has a more prominent toughness contrasted with that of bioceramics, and its elastic modulus (41–45 GPa) is closer to that of native bone contrasted with other metals. This property could assume a crucial role in avoiding the stress shielding effect. Mg also has preferable ductility over synthetic hydroxyapatite and a higher strength than existing biodegradable polymers.[247] The elastic modulus of pure Mg is nearer to that of cortical and cancellous bones, which is an unrivaled component for bone scaffolds, further indicating their vast potential for load-bearing maxillofacial bone regeneration. Mechanical characteristics of Mg could be further enhanced by alloying and thermo-mechanical methods. The addition of

alloying elements, such as silver, silicon, zinc, tin, zirconium and indium, could boost both the strength and elongation of Mg alloys.[248] Moreover, some fabrication procedures, such as hot extruding, hot rolling, and equal-channel angular pressing (ECAP) could likewise improve the strength of Mg alloys, and at times, these processes can further enhance ductility.[248–250]

Random cellular Mg could be produced through powder or chip sintering (conventional, spark plasma and laser assisted), low pressure casting, or removable spacer techniques. These production methods create a random cell framework, wide distributions of cell size, and morphology, giving rise to unpredictable material characteristics over the range of 100 μm.[225,251] Processes that could be employed to produce Mg with a topologically ordered open cell framework include the space holder technique, solid free-form process, replication, leaching technique, electrodeposition, and vapor deposition. Fig. 5 displays an example of porous Mg scaffolds fabricated by two different methods.[225]

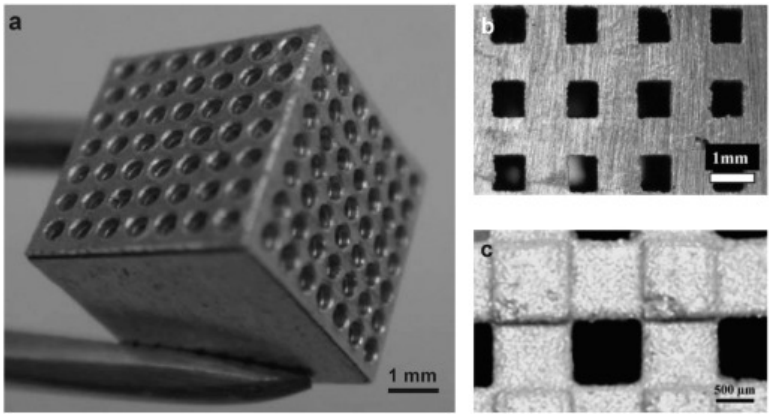

Fig. 5. Porous Mg scaffolds: (a) fabricated by laser-assisted mechanical perforation method;[283] (b, c) produced by solid free-form fabrication technique.[284]

3.2. Stem cells

The incorporation of mesenchymal stem cells (MSCs) in bone regeneration scaffolds has revolutionized the role of tissue engineering in medicine and dentistry. Their osteogenic capacity has demonstrated osteoprogenitor differentiation, osteoblast proliferation, and matrix deposition *in vitro* and *in vivo*.[252–254] MSCs also display diversity in clinical applications *via* proven acceleration in repair of femoral, craniomaxillofacial, and spinal defects, especially in animal models.[255–257] These cells also heavily increase the osteoinductive potential of scaffold biomaterials by promoting osteogenic factor activity, and they influence the surrounding microenvironment with pressure cues that are favorable for mineral deposition and bone formation, in addition to angiogenesis of the

implant for increased blood flow and nutrient diffusion to the newly formed tissue.[258–260] Mauney et al. mention that although efforts to conduct *ex vivo* expansion limit the differentiation potential of MSCs, the addition of certain growth factors, such as FGF-2, ultimately assist in retaining these properties.[261] Because of the previous body of work committed to utilizing the enormous potential of these stem cells, their mention in this paper is beneficial to potential approaches in load-bearing mandible regeneration scaffolds.

3.3. Growth factors

Similar to its their uses in cartilage regeneration, growth factors play a vital role in bone reconstruction due to their ability to elicit cellular responses and direct ligand-receptor binding that can positively impact osteogenic activity.[262] Transforming growth factor-β (TGF-β) has been used for many decades for not only osteoblast differentiation but also the activity of mesenchymal cells and production of ECM.[263] Because of its popularity and widespread use in animal models over the years, TGF-β is an ideal growth factor candidate for regenerative therapy in the craniomaxillofacial complex.[264,265] Another highly noteworthy growth factor is bone morphogenetic protein (BMP). They are the most widely studied osteogenic agents for bone synthesis in large defects.[266,267] With over 30 isoforms, the BMP family is effective in both the embryonic phase and adulthood and is unlimited in its availability in the recombinant form.[268] Intraoral and craniofacial bone repair has been investigated with recombinant human BMP (rhBMP), but human clinical trials are still limited.[266] Other growth factors, such as insulin-like growth factor (IGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF), have also been employed and studied as potent molecules for bone defects.[269]

4. Newest progress in maxillofacial tissue regeneration

Two decades ago, Sachs et al. developed a novel method of tissue fabrication in 3-dimensional bioprinting.[270] This rapid prototyping technique serves as an efficient way to design and manufacture reproducible, commercializable, and cost-efficient scaffolds in high volumes.[271] While the type of material printed a few decades ago was limited to metals and ceramics, polymers and composites have recently been used to optimize mechanical properties or bioactivity in addition to maintaining scaffold biocompatibility.[272–274]

Three-dimensional bioprinting can be manipulated with different biomaterials or varying manufacturing techniques, such as extrusion and laser-assisted sintering. Gross

macroanatomical structures can be designed by CAD data and the internal geometry can similarly be regulated by changing scaffold strand width and porosity.[275]

Bone tissue development by three-dimensional printing does not only necessitate mimicry of the original bone architecture but stable functionality as well. It is essential that the printed vascularized bone scaffolds integrate into the native tissue by allowing for nutrient diffusion and cell migration while maintaining homeostatic angiogenesis.[276] Depending on the type of biomaterial employed, the temperature can be varied in the bioprinting method to incorporate bioactive agents and drugs.[277]

In vivo bone substitutes fabricated by 3-D printing have been tested and reported in the literature with a common underlying goal of optimizing the mechanical properties, such as compressive strength, to match those of the cranium. Orthotopic examples of *in vivo* implantation have been noted in rabbits and dogs, and although craniofacial implants did yield some degree of calvarial regeneration in rabbits, the samples differed in regenerative consistency due to differences in blood supply patterns in the region.[278,279] Klammert et al. experimented with craniofacial ceramic implants in dogs, as noted above, and observed the degradation of secondary phosphate phases.[279] These two studies demonstrate that a multitude of factors play a role in optimal scaffold fabrication. Wang et al. even modified bioceramic scaffolds by filling it with a phage nanofibers to form a virus-activated matrix, which was also seeded with MSCs, and successful bone synthesis was seen as a result of osteoprogenitor differentiation, increased endothelial cell activity and stimulated angiogenesis.[280] These positive *in vivo* results show promise in the future of regenerative medicine as clinicians and research scientists work together in order to produce the most ideal scaffold for human craniofacial defect repair.

In a recent 2016 study by Kang et al., it was proven that craniofacial reconstruction, specifically biofabrication of the ear and mandible, can be achieved by means of the 3D printing process.[281] Varying concentrations of the hydrogel composite were tested for optimal cell delivery and viability as well as suitable mechanical properties. The design of their ear construct was planned intricately, maneuvering the printing process in a way that oriented synthetic PCL in certain layers and the cell-laden hydrogel in others to confer an ideal mechanical stability to the structure and fabricate microchannels that allow for the passage of nutrients and oxygen. Their handling methods of mandibular and calvarial defects differed in that they assessed that mandibular defects are arbitrary and so, dispensing paths of the composite hydrogel need to be determined with a CAD-based motion program. With regard to calvarial defects, which typically result from injury or trauma, they took the mandibular test one step further by conducting *in vivo* trials in rats

with the 3D printed bone sample and observed the sample exhibited vascularized bone growth in the central portion and periphery alike (Figs. 6 and 7).[281]

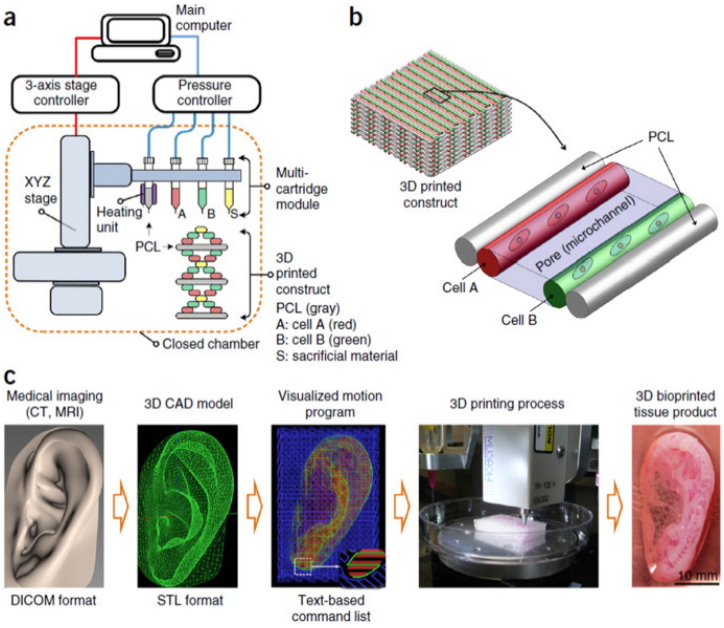

Fig. 6. Integrated tissue organ printer (ITOP) system. (a) The ITOP system consists of three main units: (i) 3-axis stage/controller, (ii) dispensing module containing multi-cartridge and pneumatic pressure controller and (iii) a closed acrylic chamber with temperature controller and humidifier. (b) Illustration of basic patterning of 3D architecture containing multiple cell-laden hydrogels and supporting polycaprolactone polymer. (c) CAD/CAM process for automated printing of 3D shape imitating target tissue/organ. A 3D CAD model yielded from medical image data produces a visualized motion program, which contains details for XYZ stage movements and actuating pneumatic pressure to generate 3D printing operations.[281]

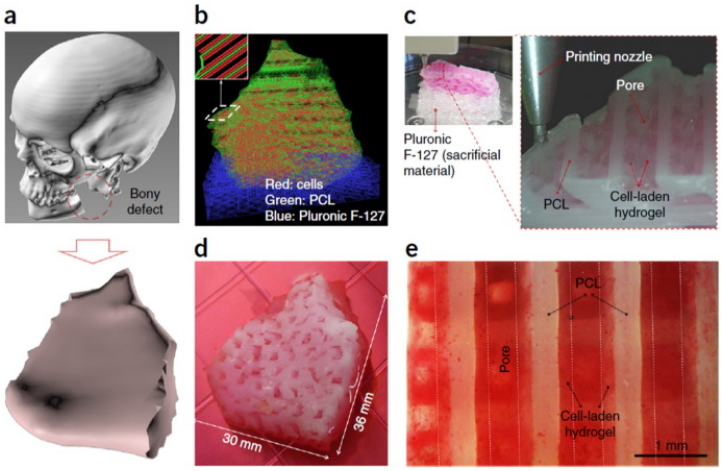

Fig. 7. Mandible bone reconstruction. (a) 3D CAD model identified a mandible bony defect from human CT image data. (b) Visualized motion program was developed to construct a 3D architecture of the mandible bone defect utilizing CAM software. Lines of green, blue and red colors show the dispensing

paths of PCL, Pluronic F-127 and cell-laden hydrogel, respectively. (c) 3D printing process utilizing the integrated organ printing system. The image displays patterning of a layer of the construct. (d) Image of the 3D printed mandible bone defect construct, which was cultured in osteogenic medium for 28 days. (e) Osteogenic differentiation of hAFSCs in the printed construct was demonstrated by Alizarin Red S staining, designating calcium deposition.[281]

Wang et al. also expanded on the previous work of experts in the field of regenerative medicine by introducing anti-inflammation functionality with the incorporation of Atsttrin, which suppresses TNF-α signaling, into an alginate/nano-hydroxyapatite scaffold.[282] The pro-inflammatory factor was known to stagnate the process of tissue regeneration by interfering with osteoblastic differentiation. By adding Atsttrin to the scaffold, superior osteogenesis was observed in mouse calvarial defects compared to the control and other experimental groups. Wang et al. ascertained that not only can 3D printed scaffolds yield calvarial bone regeneration *in vivo* but the incorporation of bioactive agents can undoubtedly have a stimulatory effect on the repair of defected tissue.[282]

5. Conclusions

Over the last decade or so, the significant rise in hard and soft tissue engineering applications has drawn the attention of experts in the fields of medicine, dentistry, bioengineering, and materials science. Great strides have been made to improve on previous results to replenish large numbers of cells and bioactive agents that ultimately give rise to newly formed tissue. Scaffold-based regeneration with the use of an abundant variety of biomaterials, in addition to stem cell and growth factor use, has proven to efficaciously restore the microanatomy and functionality of bone and cartilage tissue both *in vitro* and *in vivo*, and these results are surely paving the way for future clinical trials that are patient-specific and cost effective.

Studies of tissue engineering methods in the realm of oral and maxillofacial surgery have demonstrated that different scaffolds, polymeric, ceramic or composite, can be employed in load-bearing applications in the craniomaxillofacial complex. Their potency in revitalizing bone and cartilage in not only this region but also the entire human body provide promise and vast potential in future widespread incorporation in the defects of different maxillofacial tissues. Moreover, the expanding field of materials science is allowing bioengineers and clinicians to manufacture scaffolds of varying materials and composites that are ultimately proving to be effective in the regeneration of bone and cartilage. The evidence provided by this interdisciplinary, therapeutic approach that has

the potential to target maxillofacial anomalies provides the medical community with enthusiasm to advance the treatment of patients in a safe and effective fashion.

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References

[1]E. Alsberg, E. Hill, D. Mooney. **Craniofacial tissue engineering.** *Crit. Rev. Oral Biol. Med.*, 12 (1) (2001), pp. 64-75

[2]P. Bajpai. **Biodegradable scaffolds in orthopedic, oral and maxillofacial surgery.** *Biomater. Reconstr. Surg.,* 312–28 (1983)

[3]J. Hollinger, A. Chaudhari. **Bone regeneration materials for the mandibular and craniofacial complex.** *Cell Mater.*, 2 (2) (1992), pp. 143-151

[4]M. Mozafari, F. Moztarzadeh, M. Rabiee, M. Azami, N. Nezafati, Z. Moztarzadeh, *et al.* **Development of 3D bioactive nanocomposite scaffolds made from gelatin and NANO bioactive glass for biomedical applications.** *Adv. Compos. Lett.*, 19 (2) (2010), pp. 91-96

[5]M. Ashuri, F. Moztarzadeh, N. Nezafati, A.A. Hamedani, M. Tahriri. **Development of a composite based on hydroxyapatite and magnesium and zinc-containing sol–gel-derived bioactive glass for bone substitute applications.** *Mater. Sci. Eng.* C, 32 (8) (2012), pp. 2330-2339

[6]A. Zamanian, F. Moztarzadeh, S. Kordestani, S. Hesaraki, M. Tahriri. **Novel calcium hydroxide/nanohydroxyapatite composites for dental applications: in vitro study.** *Adv. Appl. Ceram.,* 109 (7) (2010), pp. 440-444

[7]S. Poursamar, M. Rabiee, A. Samadikuchaksaraei, M. Tahriri, M. Karimi, M. Azami. **Influence of the value of the pH on the preparation of nano hydroxyapatite polyvinyl alcohol composites.** *J. Ceram. Process. Res.*, 10 (5) (2009), pp. 679-682

[8]M. Tahriri, F. Moztarzadeh. **Preparation, characterization, and in vitro biological evaluation of PLGA/nano-fluorohydroxyapatite (FHA) microsphere-sintered scaffolds for biomedical applications.** *Appl. Biochem. Biotechnol.*, 172 (5) (2014), pp. 2465-2479

[9]M. Azami, F. Moztarzadeh, M. Tahriri. **Preparation, characterization and mechanical properties of controlled porous gelatin/hydroxyapatite nanocomposite through layer solvent casting combined with freeze-drying and lamination techniques.** *J. Porous. Mater.*, 17 (3) (2010), pp. 313-320

[10]S. Ayati Najafabadi, H. Keshvari, Y. Ganji, M. Tahriri, M. Ashuri. **Chitosan/heparin surface modified polyacrylic acid grafted polyurethane film by two step plasma treatment.** *Surf. Eng.,* 28 (9) (2012), pp. 710-714

[11]M.D. Fahmy, H.E. Jazayeri, M. Razavi, R. Masri, L. Tayebi. **Three-dimensional bioprinting materials with potential application in preprosthetic surgery.** *J. Prosthodont.* (2016)

[12]M. Kabiri, S.H. Emami, M. Rafinia, M. Tahriri. **Preparation and characterization of absorbable hemostat crosslinked gelatin sponges for surgical applications.** *Curr. Appl. Phys.*, 11 (3) (2011), pp. 457-461

[13]H. Nojehdehian, F. Moztarzadeh, H. Baharvand, N.Z. Mehrjerdi, H. Nazarian, M. Tahriri. **Effect of poly-l-lysine coating on retinoic acid-loaded PLGA microspheres in the differentiation of carcinoma stem cells into neural cells.** *Int. J. Artif. Organs*, 33 (10) (2010), pp. 721-730

[14]I. Manavi-Tehrani, M. Rabiee, M. Parviz, M.R. Tahriri, Z. Fahimi. **Preparation, characterization and controlled release investigation of biocompatible pH-sensitive PVA/PAA hydrogels.** *Macromol. Symp.*, 296 (1) (2010), pp. 457-465

[15]S.H. Emami, A.M.A. Abad, S. Bonakdar, M.R. Tahriri, A. Samadikuchaksaraei, M.A. Bahar. **Preparation and evaluation of chitosan-gelatin composite scaffolds modified with chondroitin-6-sulphate**. *Int. J. Mater. Res.*, 101 (10) (2010), pp. 1281-1285

[16]R. Touri, F. Moztarzadeh, Z. Sadeghian, D. Bizari, M. Tahriri, M. Mozafari. **The use of carbon nanotubes to reinforce 45S5 bioglass-based scaffolds for tissue engineering applications.** *Biomed. Res. Int.,* 2013 (2013)

[17]D. Bizari, F. Moztarzadeh, M. Rabiee, M. Tahriri, F. Banafatizadeh, A. Ansari, *et al.* **Development of biphasic hydroxyapatite/dicalcium phosphate dihydrate (DCPD) bone graft using polyurethane foam template: in vitro and in vivo study.** *Adv. Appl. Ceram.*, 110 (7) (2011), pp. 417-425

[18]S.A.A. Najafabadi, H. Keshvari, H. Sarkhosh, M. Ashuri, M. Tahriri. **Surface modification of castor oil-based polyurethane by polyacrylic acid graft using a two-step plasma treatment for biomedical applications.** *Adv. Polym. Technol.*, 33 (3) (2014)

[19]Y. Zamani, M. Rabiee, M.A. Shokrgozar, S. Bonakdar, M. Tahriri. **Response of human mesenchymal stem cells to patterned and randomly oriented poly (vinyl alcohol) nano-fibrous scaffolds surface-modified with Arg-Gly-Asp (RGD) ligand.** *Appl. Biochem. Biotechnol.*, 171 (6) (2013), pp. 1513-1524

[20]R. Masaeli, T.J. Kashi, R. Dinarvand, H.V. Rakhshan, B. Hooshmand, F.M. Abbas, *et al.* **Efficacy of calcium phosphate cement enhanced with 3 wt%-nanostrontium-hydroxyapatite, and nanostrontium-CPC-incorporated simvastatin-loaded poly (lactic-*co*-glycolic-acid) microspheres in bone formation: an explorative multi-phase experimental in-vitro/in-vivo study.** *Mater. Sci. Eng. C* (2016)

[21]M. Haghbin-Nazarpak, F. Moztarzadeh, M. Solati-Hashjin, M. Tahriri, K. Khoshroo. **Injectable and bioresorbable calcium phosphate delivery system with gentamicin sulphate for treatment of bone diseases: in vitro study.** *Adv. Appl. Ceram.*, 110 (8) (2011), pp. 482-489

[22]E. Sharifi Sedeh, S. Mirdamadi, F. Sharifianjazi, M. Tahriri. **Synthesis and evaluation of mechanical and biological properties of scaffold prepared from Ti and Mg with different volume percent.** *Synth. React. Inorg., Met.-Org., Nano-Met. Chem.*, 45 (7) (2015), pp. 1087-1091

[23]S. Naghavi Alhosseini, F. Moztarzadeh, S. Kargozar, M. Dodel, M. Tahriri. **Development of polyvinyl alcohol fibrous biodegradable scaffolds for nerve tissue engineering applications: in vitro study.** *Int. J. Polym. Mater. Polym. Biomater.*, 64 (9) (2015), pp. 474-480

[24]A.A. Hamedani, F. Moztarzadeh, D. Bizari, M. Ashuri, M. Tahriri. **Ion release behavior and apatite-forming ability of sol-gel derived 70S30C bioactive glass with magnesium/zinc substitution.** *Key Eng. Mater.*, 1463 (493) (2011), p. 55

[25]R. Ravarian, F. Moztarzadeh, M.S. Hashjin, S. Rabiee, P. Khoshakhlagh, M. Tahriri. **Synthesis, characterization and bioactivity investigation of bioglass/hydroxyapatite composite.** *Ceram. Int.,* 36 (1) (2010), pp. 291-297

[26]M. Mozafari, F. Moztarzadeh, M. Rabiee, M. Azami, S. Maleknia, M. Tahriri, *et al.* **Development of macroporous nanocomposite scaffolds of gelatin/bioactive glass prepared through layer solvent casting combined with lamination technique for bone tissue engineering.** *Ceram. Int.,* 36 (8) (2010), pp. 2431-2439

[27]H. Nojehdehian, F. Moztarzadeh, H. Baharvand, H. Nazarian, M. Tahriri. **Preparation and surface characterization of poly-l-lysine-coated PLGA microsphere scaffolds containing retinoic acid for nerve tissue engineering: in vitro study.** *Colloids Surf. B: Biointerfaces*, 73 (1) (2009), pp. 23-29

[28]M. Rezvannia, F. Moztarzadeh, M. Tahriri. **Formation of hydroxyapatite nanoneedles on the surface of a novel calcium phosphate/blood plasma proteins biocement in simulated body fluid (SBF).** *J. Ceram. Process. Res.*, 10 (5) (2009), pp. 669-673

[29]S. Solgi, M. Shahrezaee, A. Zamanian, T. Jafarzadeh Kashi, M. Raz, K. Khoshroo, *et al.* **Sol-gel synthesis and characterization of SiO2-Cao-P2O5-SrO bioactive glass: in vitro study.** *Key Engineering Materials*, 2015, Trans Tech Publications (2015), pp. 30-35

[30]M. Tahriri, M. Solati-Hashjin, H. Eslami. **Synthesis and characterization of hydroxyapatite nanocrystals via chemical precipitation technique.** *Iran. J. Pharm. Sci.,* 4 (2) (2008), pp. 127-134

[31]S.S. Seyedmomeni, M. Naeimi, M. Raz, J.A. Mohandesi, F. Moztarzadeh, F. Baghbani, *et al.* **Synthesis, characterization and biological evaluation of a new sol-gel derived B and Zn-containing bioactive glass: in vitro study.** *SILICON*, 1-7 (2016)

[32]M. Ashuri, F. Moztarzadeh, N. Nezafati, A.A. Hamedani, M. Tahriri. ***Synthesis and Evaluation of Mechanical Properties of Hydroxyapatite/Sol-gel Derived Bioactive Glass Particles Composites.*** (2012)

[33]S. Solgi, M. Khakbiz, M. Shahrezaee, A. Zamanian, M. Tahriri, S. Keshtkari, *et al.* **Synthesis, characterization and in vitro biological evaluation of sol-gel derived sr-containing nano bioactive glass.** *SILICON*, 1-8 (2015)

[34]T. Hooshmand, A. Abrishamchian, F. Najafi, M. Mohammadi, H. Najafi, M. Tahriri. **Development of sol-gel-derived multi-wall carbon nanotube/hydroxyapatite nanocomposite powders for bone substitution.** *J. Compos. Mater.*, 48 (4) (2013), pp. 483-489

[35]E. Salahinejad, M. Hadianfard, D. Macdonald, M. Mozafari, D. Vashaee, L. Tayebi. **Zirconium titanate thin film prepared by an aqueous particulate sol–gel spin coating process using carboxymethyl cellulose as dispersant.** *Mater. Lett.,* 88 (2012), pp. 5-8

[36]M. Mozafari, D. Vashaee, L. Tayebi, M. Mehraien. ***Electroconductive Nanocomposite Scaffolds: a New Strategy Into Tissue Engineering and Regenerative Medicine.*** INTECH Open Access Publisher (2012)

[37]M. Yazdimamaghani, M. Razavi, D. Vashaee, L. Tayebi. **Surface modification of biodegradable porous Mg bone scaffold using polycaprolactone/bioactive glass composite.** *Mater. Sci. Eng. C,* 49 (2015), pp. 436-444

[38]M. Razavi, M.H. Fathi, O. Savabi, D. Vashaee, L. Tayebi. **Biodegradation, bioactivity and in vivo biocompatibility analysis of plasma electrolytic oxidized (PEO) biodegradable Mg implants.** *Phys. Sci. Int. J.,* 4 (5) (2014), p. 708

[39]V. Shabafrooz, M. Mozafari, G.A. Köhler, S. Assefa, D. Vashaee, L. Tayebi. **The effect of hyaluronic acid on biofunctionality of gelatin–collagen intestine tissue engineering scaffolds.** *J. Biomed. Mater. Res. A,* 102 (9) (2014), pp. 3130-3139

[40]A. Tahmasbi Rad, N. Ali, H.S.R. Kotturi, M. Yazdimamaghani, J. Smay, D. Vashaee, *et al.* **Conducting scaffolds for liver tissue engineering.** *J. Biomed. Mater. Res. A,* 102 (11) (2014), pp. 4169-4181

[41]E. Salahinejad, M. Hadianfard, D. Macdonald, I. Karimi, D. Vashaee, L. Tayebi. **Aqueous sol–gel synthesis of zirconium titanate (ZrTiO 4) nanoparticles using chloride precursors.** *Ceram. Int.,* 38 (8) (2012), pp. 6145-6149

[42]E. Salahinejad, M. Hadianfard, D. Macdonald, M. Mozafari, D. Vashaee, L. Tayebi. **Multilayer zirconium titanate thin films prepared by a sol–gel deposition method.** *Ceram. Int.,* 39 (2) (2013), pp. 1271-1276

[43]M. Yazdimamaghani, D. Vashaee, S. Assefa, M. Shabrangharehdasht, A.T. Rad, M.A. Eastman, *et al.* **Green synthesis of a new gelatin-based antimicrobial scaffold for tissue engineering.** *Mater. Sci. Eng. C,* 39 (2014), pp. 235-244

[44]M. Razavi, M. Fathi, O. Savabi, S.M. Razavi, F. Heidari, M. Manshaei, *et al.* **In vivo study of nanostructured diopside (CaMgSi 2 O 6) coating on magnesium alloy as biodegradable orthopedic implants.** *Appl. Surf. Sci.,* 313 (2014), pp. 60-66

[45]M. Razavi, M. Fathi, O. Savabi, D. Vashaee, L. Tayebi. **Biodegradable magnesium alloy coated by fluoridated hydroxyapatite using MAO/EPD technique.** *Surf. Eng.,* 30 (8) (2014), pp. 545-551

[46]M. Yazdimamaghani, M. Razavi, D. Vashaee, V.R. Pothineni, J. Rajadas, L. Tayebi. **Significant degradability enhancement in multilayer coating of polycaprolactone-bioactive glass/gelatin-bioactive glass on magnesium scaffold for tissue engineering applications.** *Appl. Surf. Sci.,* 338 (2015), pp. 137-145

[47]D.L. Cochran, J.M. Wozney. **Biological mediators for periodontal regeneration.** *Periodontol.* 2000, 19 (1) (1999), pp. 40-58

[48]N.A. Peppas, R. Langer. **New challenges in biomaterials.** *Science*, 263 (5154) (1994), pp. 1715-1720

[49]M. Opas. **Expression of the differentiated phenotype by epithelial cells in vitro is regulated by both biochemistry and mechanics of the substratum.** *Dev. Biol.,* 131 (2) (1989), pp. 281-293

[50]D.E. Johns, M.E. Wong, K.A. Athanasiou. **Clinically relevant cell sources for TMJ disc engineering.** *J. Dent. Res.,* 87 (6) (2008), pp. 548-552

[51]W. Shu, L. Liu, G. Bao, H. Kang. **Tissue engineering of the temporomandibular joint disc: current status and future trends.** *Int. J. Artif. Organs,* 38 (2) (2015), pp. 55-68

[52]D. Mehrotra. **TMJ bioengineering: a review.** *J. Oral Biol. Craniofac. Res.,* 3 (3) (2013), pp. 140-145

[53]M. Thomas, D. Grande, R.H. Haug. **Development of an in vitro temporomandibular joint cartilage analog.** *J. Oral Maxillofac. Surg.,* 49 (8) (1991), pp. 854-856. (discussion 57)

[54]N.M. Girdler. **In vitro synthesis and characterization of a cartilaginous meniscus grown from isolated temporomandibular chondroprogenitor cells.** *Scand. J. Rheumatol.*, 27 (6) (1998), pp. 446-453

[55]I.N. Springer, B. Fleiner, S. Jepsen, Y. Acil. **Culture of cells gained from temporomandibular joint cartilage on non-absorbable scaffolds.** *Biomaterials*, 22 (18) (2001), pp. 2569-2577

[56]W.C. Puelacher, J. Wisser, C.A. Vacanti, N.F. Ferraro, D. Jaramillo, J.P. Vacanti. **Temporomandibular joint disc replacement made by tissue-engineered growth of cartilage.** *J. Oral Maxillofac. Surg.*, 52 (11) (1994), pp. 1172-1177

[57]H.E. Jazayeri, M.D. Fahmy, M. Razavi, B.E. Stein, A. Nowman, R.M. Masri, *et al.* **Dental applications of natural-origin polymers in hard and soft tissue engineering.** *J. Prosthodont.* (2016)

[58]A.C. Aufderheide, K.A. Athanasiou. **Comparison of scaffolds and culture conditions for tissue engineering of the knee meniscus.** *Tissue Eng.*, 11 (7–8) (2005), pp. 1095-1104

[59]Y. Kinoshita, H. Maeda. **Recent developments of functional scaffolds for craniomaxillofacial bone tissue engineering applications.** *Sci. World J.*, 2013 (2013)

[60]B.T. Goh, S. Lee, H. Tideman, P.J. Stoelinga. **Mandibular reconstruction in adults: a review.** *Int. J. Oral Maxillofac. Surg.*, 37 (7) (2008), pp. 597-605

[61]R. Lanza, R. Langer, J.P. Vacanti. ***Principles of Tissue Engineering.*** Academic Press (2011)

[62]L.G. Griffith, G. Naughton. **Tissue engineering–current challenges and expanding opportunities.** *Science*, 295 (5557) (2002), pp. 1009-1014

[63]V. Willard, L. Zhang, K.A. Athanasiou. ***Tissue Engineering of the Temporomandibular Joint.*** 2011, Elsevier (2011)

[64]D.A. Grande, C. Halberstadt, G. Naughton, R. Schwartz, R. Manji. **Evaluation of matrix scaffolds for tissue engineering of articular cartilage grafts.** *J. Biomed. Mater. Res.*, 34 (2) (1997), pp. 211-220

[65]A. Funayama, Y. Niki, H. Matsumoto, S. Maeno, T. Yatabe, H. Morioka, *et al.* **Repair of full-thickness articular cartilage defects using injectable type II collagen gel embedded with cultured chondrocytes in a rabbit model.** *J. Orthop. Sci.,* 13 (3) (2008), pp. 225-232

[66]S. Mizuno, J. Glowacki. **Three-dimensional composite of demineralized bone powder and collagen for in vitro analysis of chondroinduction of human dermal fibroblasts.** *Biomaterials*, 17 (18) (1996), pp. 1819-1825

[67]T.J. Levingstone, A. Matsiko, G.R. Dickson, F.J. O'Brien, J.P. Gleeson **A biomimetic multi-layered collagen-based scaffold for osteochondral repair** *Acta Biomater.*, 10 (5) (2014), pp. 1996-2004

[68]E. Farrell, F.J. O'Brien, P. Doyle, J. Fischer, I. Yannas, B.A. Harley, *et al.* **A collagen-glycosaminoglycan scaffold supports adult rat mesenchymal stem cell differentiation along osteogenic and chondrogenic routes** *Tissue Eng.*, 12 (3) (2006), pp. 459-468

[69]K. Tomihata, Y. Ikada **In vitro and in vivo degradation of films of chitin and its deacetylated derivatives** *Biomaterials*, 18 (7) (1997), pp. 567-575

[70]Y.-C. Kuo, C.-C. Wang **Effect of bovine pituitary extract on the formation of neocartilage in chitosan/gelatin scaffolds** *J. Taiwan Inst. Chem. Eng.*, 41 (2) (2010), pp. 150-156

[71]W.Y. Xia, W. Liu, L. Cui, Y.C. Liu, W. Zhong, D.L. Liu, *et al.* **Tissue engineering of cartilage with the use of chitosan-gelatin complex scaffolds** *J. Biomed. Mater. Res. B Appl. Biomater.*, 71B (2) (2004), pp. 373-380

[72]B. Balakrishnan, N. Joshi, A. Jayakrishnan, R. Banerjee **Self-crosslinked oxidized alginate/gelatin hydrogel as injectable, adhesive biomimetic scaffolds for cartilage regeneration** *Acta Biomater.*, 10 (8) (2014), pp. 3650-3663

[73]I.L. Kim, R.L. Mauck, J.A. Burdick **Hydrogel design for cartilage tissue engineering: a case study with hyaluronic acid** *Biomaterials*, 32 (34) (2011), pp. 8771-8782

[74]C. Chung, J.A. Burdick **Influence of three-dimensional hyaluronic acid microenvironments on mesenchymal stem cell chondrogenesis.** *Tissue Eng. A*, 15 (2) (2008), pp. 243-254

[75]H. Park, B. Choi, J. Hu, M. Lee **Injectable chitosan hyaluronic acid hydrogels for cartilage tissue engineering** *Acta Biomater.*, 9 (1) (2013), pp. 4779-4786

[76]S. Yamane, N. Iwasaki, T. Majima, T. Funakoshi, T. Masuko, K. Harada, *et al.* **Feasibility of chitosan-based hyaluronic acid hybrid biomaterial for a novel scaffold in cartilage tissue engineering** *Biomaterials*, 26 (6) (2005), pp. 611-619

[77]S.M. Willerth, S.E. Sakiyama-Elbert. ***Combining Stem Cells and Biomaterial Scaffolds for Constructing Tissues and Cell Delivery*** (2008)

[78]S.M. Willerth, K.J. Arendas, D.I. Gottlieb, S.E. Sakiyama-Elbert **Optimization of fibrin scaffolds for differentiation of murine embryonic stem cells into neural lineage cells** *Biomaterials*, 27 (36) (2006), pp. 5990-6003

[79]I. Catelas, N. Sese, B.M. Wu, J.C. Dunn, S. Helgerson, B. Tawil **Human mesenchymal stem cell proliferation and osteogenic differentiation in fibrin gels in vitro** *Tissue Eng.*, 12 (8) (2006), pp. 2385-2396

[80]O. Gurevich, A. Vexler, G. Marx, T. Prigozhina, L. Levdansky, S. Slavin, *et al* .**Fibrin microbeads for isolating and growing bone marrow-derived progenitor cells capable of forming bone tissue** *Tissue Eng.*, 8 (4) (2002), pp. 661-672

[81]G.-I. Im, Y.-W. Shin, K.-B. Lee **Do adipose tissue-derived mesenchymal stem cells have the same osteogenic and chondrogenic potential as bone marrow-derived cells?** *Osteoarthr. Cartil.*, 13 (10) (2005), pp. 845-853

[82]A.A. Worster, B.D. Brower-Toland, L.A. Fortier, S.J. Bent, J. Williams, A.J. Nixon **Chondrocytic differentiation of mesenchymal stem cells sequentially exposed to transforming growth factor-β1 in monolayer and insulin-like growth factor-I in a three-dimensional matrix** *J. Orthop. Res.*, 19 (4) (2001), pp. 738-749

[83]H. Liu, S.F. Collins, L.J. Suggs **Three-dimensional culture for expansion and differentiation of mouse embryonic stem cells** *Biomaterials*, 27 (36) (2006), pp. 6004-6014

[84]L. Meinel, V. Karageorgiou, R. Fajardo, B. Snyder, V. Shinde-Patil, L. Zichner, *et al.* **Bone tissue engineering using human mesenchymal stem cells: effects of scaffold material and medium flow** *Ann. Biomed. Eng.*, 32 (1) (2004), pp. 112-122

[85]L. Meinel, V. Karageorgiou, S. Hofmann, R. Fajardo, B. Snyder, C. Li, *et al.* **Engineering bone-like tissue in vitro using human bone marrow stem cells and silk scaffolds** *J. Biomed. Mater. Res. A*, 71 (1) (2004), pp. 25-34

[86]H.J. Kim, U.-J. Kim, G. Vunjak-Novakovic, B.-H. Min, D.L. Kaplan **Influence of macroporous protein scaffolds on bone tissue engineering from bone marrow stem cells** *Biomaterials*, 26 (21) (2005), pp. 4442-4452

[87]L. Meinel, R. Fajardo, S. Hofmann, R. Langer, J. Chen, B. Snyder, *et al.* **Silk implants for the healing of critical size bone defects** *Bone*, 37 (5) (2005), pp. 688-698

[88]H.A. Awad, M.Q. Wickham, H.A. Leddy, J.M. Gimble, F. Guilak **Chondrogenic differentiation of adipose-derived adult stem cells in agarose, alginate, and gelatin scaffolds** *Biomaterials*, 25 (16) (2004), pp. 3211-3222

[89]A.R. Finger, C.Y. Sargent, K.O. Dulaney, S.H. Bernacki, E.G. Loboa **Differential effects on messenger ribonucleic acid expression by bone marrow-derived human mesenchymal stem cells seeded in agarose constructs due to ramped and steady applications of cyclic hydrostatic pressure** *Tissue Eng.*, 13 (6) (2007), pp. 1151-1158

[90]C.Y. Charles Huang, P.M. Reuben, G. D'Ippolito, P.C. Schiller, H.S. Cheung **Chondrogenesis of human bone marrow-derived mesenchymal stem cells in agarose culture** *Anat. Rec. A: Discov. Mol. Cell. Evol. Biol.*, 278 (1) (2004), pp. 428-436

[91]S.S. Chen, W. Fitzgerald, J. Zimmerberg, H.K. Kleinman, L. Margolis **Cell-cell and cell-extracellular matrix interactions regulate embryonic stem cell differentiation** *Stem Cells*, 25 (3) (2007), pp. 553-561

[92]T. Ando, H. Yamazoe, K. Moriyasu, Y. Ueda, H. Iwata **Induction of dopamine-releasing cells from primate embryonic stem cells enclosed in agarose microcapsules** *Tissue Eng.*, 13 (10) (2007), pp. 2539-2547

[93]K. Moriyasu, H. Yamazoe, H. Iwata **Induction dopamine releasing cells from mouse embryonic stem cells and their long-term culture** *J. Biomed. Mater. Res. A*, 77 (1) (2006), pp. 136-147

[94]K. Uematsu, K. Hattori, Y. Ishimoto, J. Yamauchi, T. Habata, Y. Takakura, *et al.* **Cartilage regeneration using mesenchymal stem cells and a three-dimensional poly-lactic-glycolic acid (PLGA) scaffold** *Biomaterials*, 26 (20) (2005), pp. 4273-4279

[95]H. Fan, Y. Hu, C. Zhang, X. Li, R. Lv, L. Qin, *et al.* **Cartilage regeneration using mesenchymal stem cells and a PLGA–gelatin/chondroitin/hyaluronate hybrid scaffold** *Biomaterials*, 27 (26) (2006), pp. 4573-4580

[96]S. Kay, A. Thapa, K.M. Haberstroh, T.J. Webster **Nanostructured polymer/nanophase ceramic composites enhance osteoblast and chondrocyte adhesion** *Tissue Eng.*, 8 (5) (2002), pp. 753-761

[97]M.I. Baker, S.P. Walsh, Z. Schwartz, B.D. Boyan **A review of polyvinyl alcohol and its uses in cartilage and orthopedic applications** *J. Biomed. Mater. Res. B Appl. Biomater.*, 100 (5) (2012), pp. 1451-1457

[98]S.M. Tadavarthy, J.H. Moller, K. Amplatz **Polyvinyl alcohol (Ivalon)—a new embolic material** *Am. J. Roentgenol.*, 125 (3) (1975), pp. 609-616

[99]J.C. Bray, E.W. Merrill **Poly (vinyl alcohol) hydrogels for synthetic articular cartilage material** *J. Biomed. Mater. Res.*, 7 (5) (1973), pp. 431-443

[100]M. Kobayashi, Y.-S. Chang, M. Oka **A two year in vivo study of polyvinyl alcohol-hydrogel (PVA-H) artificial meniscus** *Biomaterials*, 26 (16) (2005), pp. 3243-3248

[101]M. Kobayashi, J. Toguchida, M. Oka **Preliminary study of polyvinyl alcohol-hydrogel (PVA-H) artificial meniscus** *Biomaterials*, 24 (4) (2003), pp. 639-647

[102]H. Bodugoz-Senturk, C.E. Macias, J.H. Kung, O.K. Muratoglu **Poly (vinyl alcohol)–acrylamide hydrogels as load-bearing cartilage substitute** *Biomaterials*, 30 (4) (2009), pp. 589-596

[103]J.A. Stammen, S. Williams, D.N. Ku, R.E. Guldberg **Mechanical properties of a novel PVA hydrogel in shear and unconfined compression** *Biomaterials*, 22 (8) (2001), pp. 799-806

[104]J.L. Holloway, K.L. Spiller, A.M. Lowman, G.R. Palmese **Analysis of the in vitro swelling behavior of poly (vinyl alcohol) hydrogels in osmotic pressure solution for soft tissue replacement** *Acta Biomater.*, 7 (6) (2011), pp. 2477-2482

[105]M.A. Shokrgozar, S. Bonakdar, M.M. Dehghan, S.H. Emami, L. Montazeri, S. Azari, *et al.* **Biological evaluation of polyvinyl alcohol hydrogel crosslinked by polyurethane chain for cartilage tissue engineering in rabbit model** *J. Mater. Sci. Mater. Med.*, 24 (10) (2013), pp. 2449-2460

[106]Y. Wu, Z. Gong, J. Li, Q. Meng, W. Fang, X. Long **The pilot study of fibrin with temporomandibular joint derived synovial stem cells in repairing TMJ disc perforation** *Biomed. Res. Int.*, 2014 (2014)

[107]K. Mäenpää, V. Ellä, J. Mauno, M. Kellomäki, R. Suuronen, T. Ylikomi, *et al.* **Use of adipose stem cells and polylactide discs for tissue engineering of the temporomandibular joint disc** *J. R. Soc. Interface*, 7 (42) (2010), pp. 177-188

[108]B.J. Costello, P. Kumta, C.S. Sfeir **Regenerative technologies for craniomaxillofacial surgery** *J. Oral Maxillofac. Surg.*, 73 (12 Suppl.) (2015), pp. S116-S125

[109]P. Sunil, R. Manikandhan, M. Muthu, S. Abraham **Stem cell therapy in oral and maxillofacial region: an overview** *J. Oral Maxillofac. Pathol.*: JOMFP, 16 (1) (2012), p. 58

[110]P.A. Zuk, M. Zhu, H. Mizuno, J. Huang, J.W. Futrell, A.J. Katz, *et al.* **Multilineage cells from human adipose tissue: implications for cell-based therapies** *Tissue Eng.*, 7 (2) (2001), pp. 211-228

[111]Y.-J. Park, S. Cha, Y.-S. Park **Regenerative applications using tooth derived stem cells in other than tooth regeneration: a literature review** *Stem Cells Int.*, 2016 (2015)

[112]S. Gronthos, M. Mankani, J. Brahim, P.G. Robey, S. Shi **Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo** *Proc. Natl. Acad. Sci.*, 97 (25) (2000), pp. 13625-13630

[113]M.T. Saito, K.G. Silvério, M.Z. Casati, E.A. Sallum, F.H. Nociti Jr. **Tooth-derived stem cells: update and perspectives** *World J. Stem Cells*, 7 (2) (2015), pp. 399-407

[114]D.L. Alge, D. Zhou, L.L. Adams, B.K. Wyss, M.D. Shadday, E.J. Woods, *et al.* **Donor-matched comparison of dental pulp stem cells and bone marrow-derived mesenchymal stem cells in a rat model** *J. Tissue Eng. Regen. Med.*, 4 (1) (2010), pp. 73-81

[115]D. Zhang, W. Jiang, M. Liu, X. Sui, X. Yin, S. Chen, *et al.* **Highly efficient differentiation of human ES cells and iPS cells into mature pancreatic insulin-producing cells** *Cell Res.*, 19 (4) (2009), pp. 429-438

[116]K. Iwasaki, M. Komaki, N. Yokoyama, Y. Tanaka, A. Taki, Y. Kimura, *et al.* **Periodontal ligament stem cells possess the characteristics of pericytes** *J. Periodontol.*, 84 (10) (2013), pp. 1425-1433

[117]N. Wada, D. Menicanin, S. Shi, P.M. Bartold, S. Gronthos **Immunomodulatory properties of human periodontal ligament stem cells** *J. Cell. Physiol.*, 219 (3) (2009), pp. 667-676

[118]L. Guo, J. Li, X. Qiao, M. Yu, W. Tang, H. Wang, *et al.* **Comparison of odontogenic differentiation of human dental follicle cells and human dental papilla cells** *PLoS One*, 8 (4) (2013), Article e62332

[119]C.M. Sedgley, T.M. Botero **Dental stem cells and their sources** *Dent. Clin. N. Am.*, 56 (3) (2012), pp. 549-561

[120]K.G. Silvério, K.C. Davidson, R.G. James, A.M. Adams, B.L. Foster, F. Nociti, *et al.* **Wnt/β-catenin pathway regulates bone morphogenetic protein (BMP2)-mediated differentiation of dental follicle cells** *J. Periodontal Res.*, 47 (3) (2012), pp. 309-319

[121]R. d'Aquino, A. De Rosa, V. Lanza, V. Tirino, L. Laino, A. Graziano, *et al.* **Human mandible bone defect repair by the grafting of dental pulp stem/progenitor cells and collagen sponge biocomplexes** *Eur. Cell. Mater.*, 18 (7) (2009), pp. 75-83

[122]A. Akkouch, Z. Zhang, M. Rouabhia **Engineering bone tissue using human dental pulp stem cells and an osteogenic collagen-hydroxyapatite-poly (l-lactide-*co*-ε-caprolactone) scaffold** *J. Biomater. Appl.*, 28 (6) (2014), pp. 922-936

[123]S. Annibali, D. Bellavia, L. Ottolenghi, A. Cicconetti, M.P. Cristalli, R. Quaranta, *et al.* **Micro-CT and PET analysis of bone regeneration induced by biodegradable scaffolds as carriers for dental pulp stem cells in a rat model of calvarial "critical size" defect: preliminary data** *J. Biomed. Mater. Res. B Appl. Biomater.*, 102 (4) (2014), pp. 815-825

[124]C. Mangano, A. De Rosa, V. Desiderio, R. d'Aquino, A. Piattelli, F. De Francesco, *et al.* **The osteoblastic differentiation of dental pulp stem cells and bone formation on different titanium surface textures** *Biomaterials*, 31 (13) (2010), pp. 3543-3551

[125]K. Kolind, D. Kraft, T. Bøggild, M. Duch, J. Lovmand, F.S. Pedersen, *et al.* **Control of proliferation and osteogenic differentiation of human dental-pulp-derived stem cells by distinct surface structures** *Acta Biomater.*, 10 (2) (2014), pp. 641-650

[126]H.-C. Liu, D.-S. Wang, F. Su, X. Wu, Z.-P. Shi, Y. Lv, *et al.* **Reconstruction of alveolar bone defects using bone morphogenetic protein 2 mediated rabbit dental pulp stem cells seeded on nano-hydroxyapatite/collagen/poly (l-lactide)** *Tissue Eng. A*, 17 (19–20) (2011), pp. 2417-2433

[127]H. Ikeda, Y. Sumita, M. Ikeda, H. Ikeda, T. Okumura, E. Sakai, *et al.* **Engineering bone formation from human dental pulp-and periodontal ligament-derived cells** *Ann. Biomed. Eng.*, 39 (1) (2011), pp. 26-34

[128]X. Yang, P. Van Der Kraan, Z. Bian, M. Fan, X. Walboomers, J. Jansen **Mineralized tissue formation by BMP2-transfected pulp stem cells** *J. Dent. Res.*, 88 (11) (2009), pp. 1020-1025

[129]X. Yang, X.F. Walboomers, J.J. van den Beucken, Z. Bian, M. Fan, J.A. Jansen **Hard tissue formation of STRO-1–selected rat dental pulp stem cells in vivo** *Tissue Eng. A*, 15 (2) (2008), pp. 367-375

[130]Y. Yamada, K. Ito, S. Nakamura, M. Ueda, T. Nagasaka **Promising cell-based therapy for bone regeneration using stem cells from deciduous teeth, dental pulp, and bone marrow** *Cell Transplant.*, 20 (7) (2011), pp. 1003-1013

[131]Y. Yamada, S. Nakamura, K. Ito, T. Sugito, R. Yoshimi, T. Nagasaka, *et al.* **A feasibility of useful cell-based therapy by bone regeneration with deciduous tooth stem cells, dental pulp stem cells, or bone-marrow-derived mesenchymal stem cells for clinical study using tissue engineering technology** *Tissue Eng. A*, 16 (6) (2010), pp. 1891-1900

[132]K. Ito, Y. Yamada, S. Nakamura, M. Ueda **Osteogenic potential of effective bone engineering using dental pulp stem cells, bone marrow stem cells, and periosteal cells for osseointegration of dental implants** *Int. J. Oral Maxillofac. Implants*, 26 (5) (2011)

[133]M. Kanafi, A. Ramesh, P. Gupta, R. Bhonde **Dental pulp stem cells immobilized in alginate microspheres for applications in bone tissue engineering** *Int. Endod. J.*, 47 (7) (2014), pp. 687-697

[134]K. Chadipiralla, J.M. Yochim, B. Bahuleyan, C.-Y.C. Huang, F. Garcia-Godoy, P.E. Murray, *et al.* **Osteogenic differentiation of stem cells derived from human periodontal ligaments and pulp of human exfoliated deciduous teeth** *Cell Tissue Res.*, 340 (2) (2010), pp. 323-333

[135]M. Tatullo, M. Marrelli, K.M. Shakesheff, L.J. White **Dental pulp stem cells: function, isolation and applications in regenerative medicine** *J. Tissue Eng. Regen. Med.*, 9 (11) (2015), pp. 1205-1216

[136]M.K. Murphy, R.F. MacBarb, M.E. Wong, K.A. Athanasiou **Temporomandibular disorders: a review of etiology, clinical management, and tissue engineering strategies** *Int. J. Oral Maxillofac. Implants*, 28 (6) (2012), pp. e393-e414

[137]A.J. Almarza, K.A. Athanasiou **Seeding techniques and scaffolding choice for tissue engineering of the temporomandibular joint disk** *Tissue Eng.*, 10 (11 − 12) (2004), pp. 1787-1795

[138]M.S. Detamore, K.A. Athanasiou **Motivation, characterization, and strategy for tissue engineering the temporomandibular joint disc** *Tissue Eng.*, 9 (6) (2003), pp. 1065-1087

[139]L.A. Fortier, G. Lust, H.O. Mohammed, A.J. Nixon **Coordinate upregulation of cartilage matrix synthesis in fibrin cultures supplemented with exogenous insulin-like growth factor-I** *J. Orthop. Res.*, 17 (4) (1999), pp. 467-474

[140]R.L. Sah, A.C. Chen, A.J. Grodzinsky, S.B. Trippel **Differential effects of bFGF and IGF-I on matrix metabolism in calf and adult bovine cartilage explants** *Arch. Biochem. Biophys.*, 308 (1) (1994), pp. 137-147

[141]T. Blunk, A.L. Sieminski, K.J. Gooch, D.L. Courter, A.P. Hollander, A.M. Nahir, *et al.* **Differential effects of growth factors on tissue-engineered cartilage** *Tissue Eng.*, 8 (1) (2002), pp. 73-84

[142]V. Tollemar, Z.J. Collier, M.K. Mohammed, M.J. Lee, G.A. Ameer, R.R. Reid **Stem cells, growth factors and scaffolds in craniofacial regenerative medicine** *Gene Dis.*, 3 (1) (2016), pp. 56-71

[143]A.R. Amini, C.T. Laurencin, S.P. Nukavarapu **Bone tissue engineering: recent advances and challenges** *Critical Reviews™ in Biomedical Engineering*, 40(5) (2012)

[144]E. Scheller, P. Krebsbach **Gene therapy: design and prospects for craniofacial regeneration** *J. Dent. Res.*, 88 (7) (2009), pp. 585-596

[145]E.L. Scheller, L.G. Villa-Diaz, P.H. Krebsbach **Gene therapy: implications for craniofacial regeneration** *J. Craniofac. Surg.*, 23 (1) (2012), p. 333

[146]A.H. Zisch, M.P. Lutolf, M. Ehrbar, G.P. Raeber, S.C. Rizzi, N. Davies, *et al.* **Cell-demanded release of VEGF from synthetic, biointeractive cell ingrowth matrices for vascularized tissue growth** *FASEB J.*, 17 (15) (2003), pp. 2260-2262

[147]M. Ehrbar, V.G. Djonov, C. Schnell, S.A. Tschanz, G. Martiny-Baron, U. Schenk, *et al.* **Cell-demanded liberation of VEGF121 from fibrin implants induces local and controlled blood vessel growth** *Circ. Res.*, 94 (8) (2004), pp. 1124-1132

[148]B.A. Fishero, N. Kohli, A. Das, J.J. Christophel, Q. Cui **Current concepts of bone tissue engineering for craniofacial bone defect repair** *Craniomaxillofac. Trauma Reconstr.*, 8 (01) (2015), pp. 023-030

[149]W. Thein-Han, J. Liu, H.H. Xu **Calcium phosphate cement with biofunctional agents and stem cell seeding for dental and craniofacial bone repair** *Dent. Mater.*, 28 (10) (2012), pp. 1059-1070

[150]M.P. Ginebra, F.C. Driessens, J.A. Planell **Effect of the particle size on the micro and nanostructural features of a calcium phosphate cement: a kinetic analysis** *Biomaterials*, 25 (17) (2004), pp. 3453-3462

[151]C.D. Friedman, P.D. Costantino, S. Takagi, L.C. Chow **BoneSource hydroxyapatite cement: a novel biomaterial for craniofacial skeletal tissue engineering and reconstruction** *J. Biomed. Mater. Res.*, 43 (4) (1998), pp. 428-432

[152]G.J. Martin Jr., S.D. Boden, M.A. Marone, M.A. Marone, P.A. Moskovitz **Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety** *J. Spinal Disord.*, 12 (3) (1999), pp. 179-186

[153]C. Bergmann, M. Lindner, W. Zhang, K. Koczur, A. Kirsten, R. Telle, *et al.* **3D printing of bone substitute implants using calcium phosphate and bioactive glasses** *J. Eur. Ceram. Soc.*, 30 (12) (2010), pp. 2563-2567

[154]J. Li, Y. Hsu, E. Luo, A. Khadka, J. Hu **Computer-aided design and manufacturing and rapid prototyped nanoscale hydroxyapatite/polyamide (n-HA/PA) construction for condylar defect caused by mandibular angle ostectomy** *Aesthet. Plast. Surg.*, 35 (4) (2011), pp. 636-640

[155]T.M. Chu, D.G. Orton, S.J. Hollister, S.E. Feinberg, J.W. Halloran **Mechanical and in vivo performance of hydroxyapatite implants with controlled architectures** *Biomaterials*, 23 (5) (2002), pp. 1283-1293

[156]J.C. Zhang, H.Y. Lu, G.Y. Lv, A.C. Mo, Y.G. Yan, C. Huang **The repair of critical-size defects with porous hydroxyapatite/polyamide nanocomposite: an experimental study in rabbit mandibles** *Int. J. Oral Maxillofac. Surg.*, 39 (5) (2010), pp. 469-477

[157]J.R. Jones **Review of bioactive glass: from Hench to hybrids** *Acta Biomater.*, 9 (1) (2013), pp. 4457-4486

[158]S.M. Rabiee, N. Nazparvar, M. Azizian, D. Vashaee, L. Tayebi **Effect of ion substitution on properties of bioactive glasses: a review** *Ceram. Int.*, 41 (6) (2015), pp. 7241-7251

[159]M. Yazdimamaghani, D. Vashaee, S. Assefa, K. Walker, S. Madihally, G. Köhler, *et al.* **Hybrid macroporous gelatin/bioactive-glass/nanosilver scaffolds with controlled degradation behavior and antimicrobial activity for bone tissue engineering** *J. Biomed. Nanotechnol.*, 10 (6) (2014), pp. 911-931

[160]A. Yazdanpanah, R. Kamalian, F. Moztarzadeh, M. Mozafari, R. Ravarian, L. Tayebi **Enhancement of fracture toughness in bioactive glass-based nanocomposites with nanocrystalline forsterite as advanced biomaterials for bone tissue engineering applications** *Ceram. Int.*, 38 (6) (2012), pp. 5007-5014

[161]L.L. Hench, R.J. Splinter, W. Allen, T. Greenlee **Bonding mechanisms at the interface of ceramic prosthetic materials** *J. Biomed. Mater. Res.*, 5 (6) (1971), pp. 117-141

[162]N.S. AboElsaad, M. Soory, L.M. Gadalla, L.I. Ragab, S. Dunne, K.R. Zalata, *et al.* **Effect of soft laser and bioactive glass on bone regeneration in the treatment of bone defects (an experimental study)** *Lasers Med. Sci.*, 24 (4) (2009), pp. 527-533

[163]V.S. Yadav, S.C. Narula, R.K. Sharma, S. Tewari, R. Yadav **Clinical evaluation of guided tissue regeneration combined with autogenous bone or autogenous bone mixed with bioactive glass in intrabony defects** *J. Oral Sci.*, 53 (4) (2011), pp. 481-488

[164]T. Turunen, J. Peltola, A. Yli-Urpo, R.P. Happonen **Bioactive glass granules as a bone adjunctive material in maxillary sinus floor augmentation** *Clin. Oral Implants Res.*, 15 (2) (2004), pp. 135-141

[165]D.G. Gillam, J.Y. Tang, N.J. Mordan, H.N. Newman **The effects of a novel bioglass dentifrice on dentine sensitivity: a scanning electron microscopy investigation** *J. Oral Rehabil.*, 29 (4) (2002), pp. 305-313

[166]B.B. Ward, S.E. Brown, P.H. Krebsbach **Bioengineering strategies for regeneration of craniofacial bone: a review of emerging technologies** *Oral Dis.*, 16 (8) (2010), pp. 709-716

[167]L.S. Karfeld-Sulzer, F.E. Weber **Biomaterial development for oral and maxillofacial bone regeneration** *J. Korean Assoc. Oral Maxillofac. Surg.*, 38 (5) (2012), pp. 264-270

[168]M. Retzepi, N. Donos **Guided bone regeneration: biological principle and therapeutic applications** *Clin. Oral Implants Res.*, 21 (6) (2010), pp. 567-576

[169]R.A. Hitti, D.G. Kerns **Guided bone regeneration in the oral cavity: a review** *Open Pathol. J.*, 5 (2011), pp. 33-45

[170]L.F. Rodella, G. Favero, M. Labanca **Biomaterials in maxillofacial surgery: membranes and grafts** *Int. J. Biomed. Sci.*, 7 (2) (2011), pp. 81-88

[171]I.A. Urban, S.A. Jovanovic, J.L. Lozada **Vertical ridge augmentation using guided bone regeneration (GBR) in three clinical scenarios prior to implant placement: a retrospective study of 35 patients 12 to 72 months after loading** *Int. J. Oral Maxillofac. Implants* (2009), p. 24(3)

[172]D. Buser, C. Dahlin, R. Schenk. ***Guided Bone Regeneration*** Quintessence, Chicago (1994)

[173]K.A. Selvig, R.E. Nilveus, L. Fitzmorris, B. Kersten, S.S. Khorsandi **Scanning electron microscopic observations of cell population and bacterial contamination of membranes used for guided periodontal tissue regeneration in humans** *J. Periodontol.*, 61 (8) (1990), pp. 515-520

[174]H.J. Grevstad, K.N. Leknes **Ultrastructure of plaque associated with polytetrafluoroethylene (PTFE) membranes used for guided tissue regeneration** *J. Clin. Periodontol.*, 20 (3) (1993), pp. 193-198

[175]S. Verardi, M. Simion **Management of the exposure of e-PTFE membranes in guided bone regeneration** *Pract. Proced. Aesthet. Dent.*: PPAD, 19 (2) (2007), pp. 111-117

[176]H.D. Barber, J. Lignelli, B.M. Smith, B.K. Bartee **Using a dense PTFE membrane without primary closure to achieve bone and tissue regeneration** *J. Oral Maxillofac. Surg.*, 65 (4) (2007), pp. 748-752

[177]J. Seibert, S. Nyman **Localized ridge augmentation in dogs: a pilot study using membranes and hydroxyapatite** *J. Periodontol.*, 61 (3) (1990), pp. 157-165

[178]M.C. Bottino, V. Thomas, G. Schmidt, Y.K. Vohra, T.-M.G. Chu, M.J. Kowolik, *et al.* **Recent advances in the development of GTR/GBR membranes for periodontal regeneration—a materials perspective** *Dent. Mater.*, 28 (7) (2012), pp. 703-721

[179]P. Gentile, V. Chiono, C. Tonda-Turo, A.M. Ferreira, G. Ciardelli **Polymeric membranes for guided bone regeneration** *Biotechnol. J.*, 6 (10) (2011), pp. 1187-1197

[180]N.C. Geurs, J.M. Korostoff, P.J. Vassilopoulos, T.-H. Kang, M. Jeffcoat, R. Kellar, *et al.* **Clinical and histologic assessment of lateral alveolar ridge augmentation using a synthetic long-term bioabsorbable membrane and an allograft** *J. Periodontol.*, 79 (7) (2008), pp. 1133-1140

[181]A. Sculean, D. Nikolidakis, F. Schwarz **Regeneration of periodontal tissues: combinations of barrier membranes and grafting materials–biological foundation and preclinical evidence: a systematic review** *J. Clin. Periodontol.*, 35 (s8) (2008), pp. 106-116

[182]E. Milella, G. Barra, P. Ramires, G. Leo, P. Aversa, A. Romito **Poly (l-lactide) acid/alginate composite membranes for guided tissue regeneration** *J. Biomed. Mater. Res.*, 57 (2) (2001), pp. 248-257

[183]H.-L. Wang, W.J. Carroll. ***Guided bone regeneration using bone grafts and collagen membranes*** Quintessence Int., 32 (7) (2001)

[184]H. Tal, A. Kozlovsky, Z. Artzi, C.E. Nemcovsky, O. Moses **Cross-linked and non-cross-linked collagen barrier membranes disintegrate following surgical exposure to the oral environment: a histological study in the cat** *Clin. Oral Implants Res.*, 19 (8) (2008), pp. 760-766

[185]R. Parodi, G. Carusi, G. Santarelli, F. Nanni **Implant placement in large edentulous ridges expanded by GBR using a bioresorbable collagen membrane** *Int. J. Periodontics Restorative Dent.*, 18 (3) (1998)

[186]P. Colangelo, A. Piattelli, S. Barrucci, P. Trisi, G. Formisano, S. Caiazza **Bone regeneration guided by resorbable collagen membranes in rabbits: a pilot study** *Implant. Dent.*, 2 (2) (1993), pp. 101-106

[187]M. Coïc, V. Placet, E. Jacquet, C. Meyer **Mechanical properties of collagen membranes used in guided bone regeneration: a comparative study of three models** *Rev. Stomatol. Chir. Maxillofac.*, 111 (5–6) (2009), pp. 286-290

[188]H.K. Makadia, S.J. Siegel **Poly lactic-*co*-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier** *Polymer*, 3 (3) (2011), pp. 1377-1397

[189]M. Vert **Aliphatic polyesters: great degradable polymers that cannot do everything** *Biomacromolecules*, 6 (2) (2005), pp. 538-546

[190]R.E. Jung, G.A. Hälg, D.S. Thoma, C.H. Hämmerle **A randomized, controlled clinical trial to evaluate a new membrane for guided bone regeneration around dental implants** *Clin. Oral Implants Res.*, 20 (2) (2009), pp. 162-168

[191]R.E. Jung, R. Zwahlen, F.E. Weber, A. Molenberg, G.H. Van Lenthe, C.H. Hammerle **Evaluation of an in situ formed synthetic hydrogel as a biodegradable membrane for guided bone regeneration** *Clin. Oral Implants Res.*, 17 (4) (2006), pp. 426-433

[192]S. Wechsler, D. Fehr, A. Molenberg, G. Raeber, J.C. Schense, F.E. Weber **A novel, tissue occlusive poly (ethylene glycol) hydrogel material** *J. Biomed. Mater. Res. A*, 85 (2) (2008), pp. 285-292

[193]J. Gottlow, S. Nyman, T. Karring, J. Lindhe **New attachment formation as the result of controlled tissue regeneration** *J. Clin. Periodontol.*, 11 (8) (1984), pp. 494-503

[194]P. Hyder, P. Dowell, G. Singh, A. Dolby **Freeze-dried, cross-linked bovine type I collagen: analysis of properties*** *J. Periodontol.*, 63 (3) (1992), pp. 182-186

[195]T. Kodama, M. Minabe, T. Hori, Y. Watanabe **The effect of various concentrations of collagen barrier on periodontal wound healing*** *J. Periodontol.*, 60 (4) (1989), pp. 205-210

[196]P.M. Robert, R.M. Frank **Periodontal guided tissue regeneration with a new resorbable polylactic acid membrane*** *J. Periodontol.*, 65 (5) (1994), pp. 414-422

[197]L. Laurell, H. Falk, J. Fornell, G. Johard, J. Gottlow **Clinical use of a bioresorbable matrix barrier in guided tissue regeneration therapy. Case series** *J. Periodontol.*, 65 (10) (1994), pp. 967-975

[198]G. Wei, P.X. Ma **Structure and properties of nano-hydroxyapatite/polymer composite scaffolds for bone tissue engineering** *Biomaterials*, 25 (19) (2004), pp. 4749-4757

[199]Y. Zhang, M. Zhang **Three-dimensional macroporous calcium phosphate bioceramics with nested chitosan sponges for load-bearing bone implants** *J. Biomed. Mater. Res.*, 61 (1) (2002), pp. 1-8

[200]C.R. Kothapalli, M.T. Shaw, M. Wei **Biodegradable HA-PLA 3-D porous scaffolds: effect of nano-sized filler content on scaffold properties** *Acta Biomater.*, 1 (6) (2005), pp. 653-662

[201]P.X. Ma, R. Zhang, G. Xiao, R. Franceschi **Engineering new bone tissue in vitro on highly porous poly(alpha-hydroxyl acids)/hydroxyapatite composite scaffolds** *J. Biomed. Mater. Res.*, 54 (2) (2001), pp. 284-293

[202]Y.W. Wang, Q. Wu, J. Chen, G.Q. Chen **Evaluation of three-dimensional scaffolds made of blends of hydroxyapatite and poly(3-hydroxybutyrate-*co*-3-hydroxyhexanoate) for bone reconstruction** *Biomaterials*, 26 (8) (2005), pp. 899-904

[203]H.H. Xu, C.G. Simon Jr. **Fast setting calcium phosphate-chitosan scaffold: mechanical properties and biocompatibility** *Biomaterials*, 26 (12) (2005), pp. 1337-1348

[204]S.S. Kim, M. Sun Park, O. Jeon, C. Yong Choi, B.S. Kim **Poly(lactide-*co*-glycolide)/hydroxyapatite composite scaffolds for bone tissue engineering** *Biomaterials*, 27 (8) (2006), pp. 1399-1409

[205]R.M. Schek, J.M. Taboas, S.J. Hollister, P.H. Krebsbach **Tissue engineering osteochondral implants for temporomandibular joint repair** *Orthod. Craniofacial Res.*, 8 (4) (2005), pp. 313-319

[206]H. Xu, D. Han, J.S. Dong, G.X. Shen, G. Chai, Z.Y. Yu, *et al.* **Rapid prototyped PGA/PLA scaffolds in the reconstruction of mandibular condyle bone defects** *Int. J. Med. Rob.*, 6 (1) (2010), pp. 66-72

[207]G. Zhou, W. Liu, L. Cui, X. Wang, T. Liu, Y. Cao **Repair of porcine articular osteochondral defects in non-weightbearing areas with autologous bone marrow stromal cells** *Tissue Eng.*, 12 (11) (2006), pp. 3209-3221

[208]R.A. Muzzarelli **Chitosan composites with inorganics, morphogenetic proteins and stem cells, for bone regeneration** *Carbohydr. Polym.*, 83 (4) (2011), pp. 1433-1445

[209]R.A.A. Muzzarelli, G. Biagini, M. Bellardini, L. Simonelli, C. Castaldini, G. Fratto **Osteoconduction exerted by methylpyrrolidinone chitosan used in dental surgery** *Biomaterials*, 14 (1) (1993), pp. 39-43

[210]C. Yang, L. Xu, Y. Zhou, X.M. Zhang, X. Huang, M. Wang, *et al.* **A green fabrication approach of gelatin/CM-chitosan hybrid hydrogel for wound healing** *Carbohydr. Polym.*, 82 (4) (2010), pp. 1297-1305

[211]Y. Zhou, L. Xu, X. Zhang, Y. Zhao, S. Wei, M. Zhai **Radiation synthesis of gelatin/CM-chitosan/β-tricalcium phosphate composite scaffold for bone tissue engineering** *Mater. Sci. Eng. C*, 32 (4) (2012), pp. 994-1000

[212]C.D. Friedman, P.D. Costantino, K. Jones, L.C. Chow, H.J. Pelzer, G.A. Sisson Sr. **Hydroxyapatite cement. II. Obliteration and reconstruction of the cat frontal sinus** *Arch. Otolaryngol. Head Neck Surg.*, 117 (4) (1991), pp. 385-389

[213]C.T. Laurencin, A.M. Ambrosio, M.D. Borden, J.A. Cooper Jr. **Tissue engineering: orthopedic applications** *Annu. Rev. Biomed. Eng.*, 1 (1999), pp. 19-46

[214]C.D. Friedman, P.D. Costantino, S. Takagi, L.C. Chow **BoneSource (TM) hydroxyapatite cement: a novel biomaterial for craniofacial skeletal tissue engineering and reconstruction** *J. Biomed. Mater. Res.*, 43 (4) (1998), pp. 428-432

[215]H.H. Xu, J.B. Quinn, S. Takagi, L.C. Chow **Synergistic reinforcement of in situ hardening calcium phosphate composite scaffold for bone tissue engineering** *Biomaterials*, 25 (6) (2004), pp. 1029-1037

[216]V. Karageorgiou, D. Kaplan **Porosity of 3D biomaterial scaffolds and osteogenesis** *Biomaterials*, 26 (27) (2005), pp. 5474-5491

[217]G.A. Fielding, A. Bandyopadhyay, S. Bose **Effects of silica and zinc oxide doping on mechanical and biological properties of 3D printed tricalcium phosphate tissue engineering scaffolds** *Dent. Mater.*, 28 (2) (2012), pp. 113-122

[218]S.S. Banerjee, S. Tarafder, N.M. Davies, A. Bandyopadhyay, S. Bose **Understanding the influence of MgO and SrO binary doping on the mechanical and biological properties of beta-TCP ceramics** *Acta Biomater.*, 6 (10) (2010), pp. 4167-4174

[219]S. Bose, S. Tarafder, S.S. Banerjee, N.M. Davies, A. Bandyopadhyay **Understanding in vivo response and mechanical property variation in MgO, SrO and SiO(2) doped beta-TCP** *Bone*, 48 (6) (2011), pp. 1282-1290

[220]R. Cavagna, G. Daculsi, J.M. Bouler **Macroporous calcium phosphate ceramic: a prospective study of 106 cases in lumbar spinal fusion** *J. Long-Term Eff. Med. Implants*, 9 (4) (1999), pp. 403-412

[221]H. Li, Y. Zheng, L. Qin **Progress of biodegradable metals** *Prog. Nat. Sci. Mater. Int.*, 24 (5) (2014), pp. 414-422

[222]N.-E.L. Saris, E. Mervaala, H. Karppanen, J.A. Khawaja, A. Lewenstam **Magnesium: an update on physiological, clinical and analytical aspects** *Clin. Chim. Acta*, 294 (1) (2000), pp. 1-26

[223]J. Vormann **Magnesium: nutrition and metabolism** *Mol. Asp. Med.*, 24 (1) (2003), pp. 27-37

[224]M.P. Staiger, A.M. Pietak, J. Huadmai, G. Dias **Magnesium and its alloys as orthopedic biomaterials: a review** *Biomaterials*, 27 (9) (2006), pp. 1728-1734

[225]A. Yusop, A. Bakir, N. Shaharom, M. Abdul Kadir, H. Hermawan **Porous biodegradable metals for hard tissue scaffolds: a review** *Int. J. Biomater.*, 2012 (2012)

[226]A. Saboori, M. Rabiee, F. Moztarzadeh, M. Sheikhi, M. Tahriri, M. Karimi **Synthesis, characterization and in vitro bioactivity of sol-gel-derived SiO 2–CaO–P 2 O 5–MgO bioglass** *Mater. Sci. Eng. C*, 29 (1) (2009), pp. 335-340

[227]Y. Rezaei, F. Moztarzadeh, S. Shahabi, M. Tahriri **Synthesis, characterization, and in vitro bioactivity of sol-gel-derived SiO2–CaO–P2O5–MgO-SrO bioactive glass** *Synth. React. Inorg., Met.-Org., Nano-Met. Chem.*, 44 (5) (2014), pp. 692-701

[228]A. Hartwig **Role of magnesium in genomic stability** *Mutat. Res. Fundam. Mol. Mech. Mutagen.*, 475 (1) (2001), pp. 113-121

[229]F.I. Wolf, A. Cittadini **Chemistry and biochemistry of magnesium** *Mol. Asp. Med.*, 24 (1) (2003), pp. 3-9

[230]R. Berkow, A. Fletcher, P. Bondy **Water, electrolyte, mineral, and acid-base metabolism** *The Merck Manual of Diagnosis and Therapy, Merck Research Laboratory*, Rahway, NJ (1992), pp. 986-1026

[231]F. Witte, V. Kaese, H. Haferkamp, E. Switzer, A. Meyer-Lindenberg, C. Wirth, *et al.* **In vivo corrosion of four magnesium alloys and the associated bone response** *Biomaterials*, 26 (17) (2005), pp. 3557-3563

[232]F. Witte, H. Crostack, J. Nellesen, F. Beckmann **Characterization of Degradable Magnesium Alloys as Orthopaedic Implant Material by Synchrotron-radiationbased Microtomography** (2012) (www-hasylab.desyde/science/annual_reports/2001_report/partl/contrib/47/5461.pdf)

[233]M. Razavi, M. Fathi, O. Savabi, S.M. Razavi, B.H. Beni, D. Vashaee, *et al.* **Surface modification of magnesium alloy implants by nanostructured bredigite coating** *Mater. Lett.*, 113 (2013), pp. 174-178

[234]M. Razavi, M. Fathi, O. Savabi, D. Vashaee, L. Tayebi **In vitro study of nanostructured diopside coating on Mg alloy orthopedic implants** *Mater. Sci. Eng. C*, 41 (2014), pp. 168-177

[235]M. Razavi, M. Fathi, O. Savabi, D. Vashaee, L. Tayebi **Regenerative influence of nanostructured bredigite (Ca 7 MgSi 4 O 16)/anodic spark coating on biodegradable AZ91 magnesium alloy implants for bone healing** *Mater. Lett.*, 155 (2015), pp. 97-101

[236]M. Razavi, M. Fathi, O. Savabi, D. Vashaee, L. Tayebi **In vivo study of nanostructured akermanite/PEO coating on biodegradable magnesium alloy for biomedical applications** *J. Biomed. Mater. Res. A*, 103 (5) (2015), pp. 1798-1808

[237]M. Razavi, M. Fathi, O. Savabi, D. Vashaee, L. Tayebi **Improvement of biodegradability, bioactivity, mechanical integrity and cytocompatibility behavior of biodegradable mg based orthopedic implants using nanostructured bredigite (Ca7MgSi4O16) bioceramic coated via ASD/EPD technique** *Ann. Biomed. Eng.*, 42 (12) (2014), pp. 2537-2550

[238]M. Razavi, M. Fathi, O. Savabi, D. Vashaee, L. Tayebi **In vivo biocompatibility of Mg implants surface modified by nanostructured merwinite/PEO** *J. Mater. Sci. Mater. Med.*, 26 (5) (2015), pp. 1-7

[239]M. Razavi, M. Fathi, O. Savabi, D. Vashaee, L. Tayebi **In vitro analysis of electrophoretic deposited fluoridated hydroxyapatite coating on micro-arc oxidized AZ91 magnesium alloy for biomaterials applications** *Metall. Mater. Trans. A*, 46 (3) (2015), pp. 1394-1404

[240]M. Razavi, M. Fathi, O. Savabi, D. Vashaee, L. Tayebi **In vitro evaluations of anodic spark deposited AZ91 alloy as biodegradable metallic orthopedic implant** *Annual Research & Review in Biology*, 4(24) (2014), p. 3716

[241]L. Xu, G. Yu, E. Zhang, F. Pan, K. Yang **In vivo corrosion behavior of Mg-Mn-Zn alloy for bone implant application** *J. Biomed. Mater. Res. A*, 83 (3) (2007), pp. 703-711

[242]F. Witte, H. Ulrich, M. Rudert, E. Willbold **Biodegradable magnesium scaffolds: part 1: appropriate inflammatory response** *J. Biomed. Mater. Res. A*, 81 (3) (2007), pp. 748-756 [243]X. Gu, W. Zhou, Y. Zheng, Y. Liu, Y. Li **Degradation and cytotoxicity of lotus-type porous pure magnesium as potential tissue engineering scaffold material** *Mater. Lett.*, 64 (17) (2010), pp. 1871-1874

[244]H. Zreiqat, C. Howlett, A. Zannettino, P. Evans, G. Schulze-Tanzil, C. Knabe, *et al.* **Mechanisms of magnesium-stimulated adhesion of osteoblastic cells to commonly used orthopaedic implants** *J. Biomed. Mater. Res.*, 62 (2) (2002), pp. 175-184

[245]Y. Yamasaki, Y. Yoshida, M. Okazaki, A. Shimazu, T. Uchida, T. Kubo, *et al.* **Synthesis of functionally graded MgCO3 apatite accelerating osteoblast adhesion** *J. Biomed. Mater. Res.*, 62 (1) (2002), pp. 99-105

[246]Y. Yamasaki, Y. Yoshida, M. Okazaki, A. Shimazu, T. Kubo, Y. Akagawa, *et al.* **Action of FGMgCO 3 Ap-collagen composite in promoting bone formation** *Biomaterials*, 24 (27) (2003), pp. 4913-4920

[247]X.-N. Gu, Y.-F. Zheng **A review on magnesium alloys as biodegradable materials** *Front. Mater. Sci. Chin.*, 4 (2) (2010), pp. 111-115

[248]X. Gu, Y. Zheng, Y. Cheng, S. Zhong, T. Xi **In vitro corrosion and biocompatibility of binary magnesium alloys** *Biomaterials*, 30 (4) (2009), pp. 484-498

[249]H. Wang, Y. Estrin, Z. Zúberová **Bio-corrosion of a magnesium alloy with different processing histories** *Mater. Lett.*, 62 (16) (2008), pp. 2476-2479

[250]Z. Li, X. Gu, S. Lou, Y. Zheng **The development of binary Mg–Ca alloys for use as biodegradable materials within bone** *Biomaterials*, 29 (10) (2008), pp. 1329-1344

[251]T. Adachi, Y. Osako, M. Tanaka, M. Hojo, S.J. Hollister **Framework for optimal design of porous scaffold microstructure by computational simulation of bone regeneration** *Biomaterials*, 27 (21) (2006), pp. 3964-3972

[252]D.C. Colter, I. Sekiya, D.J. Prockop **Identification of a subpopulation of rapidly self-renewing and multipotential adult stem cells in colonies of human marrow stromal cells** *Proc. Natl. Acad. Sci.*, 98 (14) (2001), pp. 7841-7845

[253]J.A. Andrades, J.A. Santamaria, M.E. Nimni, J. Becerra **Selection and amplification of a bone marrow cell population and its induction to the chondro-osteogenic lineage by rhOP-1: an in vitro and in vivo study** *Int. J. Dev. Biol.*, 45 (4) (2001), pp. 689-693

[254]T.L. Arinzeh, S.J. Peter, M.P. Archambault, C. Van Den Bos, S. Gordon, K. Kraus, *et al.* **Allogeneic mesenchymal stem cells regenerate bone in a critical-sized canine segmental defect** *J. Bone Joint Surg. Am.*, 85 (10) (2003), pp. 1927-1935

[255]H. Petite, V. Viateau, W. Bensaid, A. Meunier, C. de Pollak, M. Bourguignon, *et al.* **Tissue-engineered bone regeneration** *Nat. Biotechnol.*, 18 (9) (2000), pp. 959-963

[256]E. Kon, A. Muraglia, A. Corsi, P. Bianco, M. Marcacci, I. Martin, *et al.* **Autologous bone marrow stromal cells loaded onto porous hydroxyapatite ceramic accelerate bone repair in critical-size defects of sheep long bones** *J. Biomed. Mater. Res.*, 49 (3) (2000), pp. 328-337

[257]Q. Shang, Z. Wang, W. Liu, Y. Shi, L. Cui, Y. Cao **Tissue-engineered bone repair of sheep cranial defects with autologous bone marrow stromal cells** *J. Craniofac. Surg.*, 12 (6) (2001), pp. 586-593 (discussion 94-5)

[258]M. Kruyt, J. De Bruijn, C. Wilson, F. Oner, C. Van Blitterswijk, A. Verbout, *et al.* **Viable osteogenic cells are obligatory for tissue-engineered ectopic bone formation in goats** *Tissue Eng.*, 9 (2) (2003), pp. 327-336

[259]D. Levin, D. Norman, C. Zinman, L. Rubinstein, E. Sabo, I. Misselevich, *et al.* **Treatment of experimental avascular necrosis of the femoral head with hyperbaric oxygen in rats: histological evaluation of the femoral heads during the early phase of the reparative process** *Exp. Mol. Pathol.*, 67 (2) (1999), pp. 99-108

[260]P. Pelissier, F. Villars, S. Mathoulin-Pelissier, R. Bareille, M.-H. Lafage-Proust, J. Vilamitjana-Amedee **Influences of vascularization and osteogenic cells on heterotopic bone formation within a madreporic ceramic in rats** *Plast. Reconstr. Surg.*, 111 (6) (2003), pp. 1932-1941

[261]J.R. Mauney, V. Volloch, D.L. Kaplan **Role of adult mesenchymal stem cells in bone tissue engineering applications: current status and future prospects** *Tissue Eng.*, 11 (5–6) (2005), pp. 787-802

[262]K. Lee, E.A. Silva, D.J. Mooney **Growth factor delivery-based tissue engineering: general approaches and a review of recent developments** *J. R. Soc. Interface*, 8 (55) (2011), pp. 153-170

[263]A.J. Celeste, J.A. Iannazzi, R.C. Taylor, R.M. Hewick, V. Rosen, E.A. Wang, *et al.* **Identification of transforming growth factor beta family members present in bone-inductive protein purified from bovine bone** *Proc. Natl. Acad. Sci.*, 87 (24) (1990), pp. 9843-9847

[264]D. Nikolidakis, G.J. Meijer, D.A. Oortgiesen, X.F. Walboomers, J.A. Jansen **The effect of a low dose of transforming growth factor β1 (TGF-β1) on the early bone-healing around oral implants inserted in trabecular bone** *Biomaterials*, 30 (1) (2009), pp. 94-99

[265]H. Ueda, L. Hong, M. Yamamoto, K. Shigeno, M. Inoue, T. Toba, *et al.* **Use of collagen sponge incorporating transforming growth factor-β1 to promote bone repair in skull defects in rabbits** *Biomaterials*, 23 (4) (2002), pp. 1003-1010

[266]J. Fischer, A. Kolk, C. Pautke, P. Warnke, C. Plank, R. Smeets **Future of local bone regeneration–protein versus gene therapy** *J. Cranio-Maxillofac. Surg.*, 39 (1) (2011), pp. 54-64

[267]N. Kimelman, G. Pelled, G.A. Helm, J. Huard, E.M. Schwarz, D. Gazit **Review: gene-and stem cell-based therapeutics for bone regeneration and repair** *Tissue Eng.*, 13 (6) (2007), pp. 1135-1150

[268]C.A. Kirker-Head **Potential applications and delivery strategies for bone morphogenetic proteins** *Adv. Drug Deliv. Rev.*, 43 (1) (2000), pp. 65-92

[269]S.-H. Lee, H. Shin **Matrices and scaffolds for delivery of bioactive molecules in bone and cartilage tissue engineering** *Adv. Drug Deliv. Rev.*, 59 (4) (2007), pp. 339-359

[270]E. Sachs, M. Cima, P. Williams, D. Brancazio, J. Cornie **3-Dimensional printing–rapid tooling and prototypes directly from a cad model** *J. Eng. Ind. Trans. ASME*, 114 (4) (1992), pp. 481-488

[271]S. Bose, S. Vahabzadeh, A. Bandyopadhyay **Bone tissue engineering using 3D printing** *Mater. Today*, 16 (12) (2013), pp. 496-504

[272]E. Sachs, M. Cima, P. Williams, D. Brancazio, J. Cornie **Three dimensional printing: rapid tooling and prototypes directly from a CAD model** *J. Eng. Ind.*, 114 (4) (1992), pp. 481-488

[273]H. Seitz, W. Rieder, S. Irsen, B. Leukers, C. Tille **Three-dimensional printing of porous ceramic scaffolds for bone tissue engineering** *J. Biomed. Mater. Res. B Appl. Biomater.*, 74 (2) (2005), pp. 782-788

[274]R. Detsch, S. Schaefer, U. Deisinger, G. Ziegler, H. Seitz, B. Leukers **In vitro-osteoclastic activity studies on surfaces of 3D printed calcium phosphate scaffolds** *J. Biomater. Appl.* (2010)

[275]R. Tevlin, A. McArdle, D. Atashroo, G. Walmsley, K. Senarath-Yapa, E. Zielins, *et al.* **Biomaterials for craniofacial bone engineering** *J. Dent. Res.*, 93 (12) (2014), pp. 1187-1195

[276]N.E. Fedorovich, J. Alblas, W.E. Hennink, F.C. Öner, W.J. Dhert **Organ printing: the future of bone regeneration?** *Trends Biotechnol.*, 29 (12) (2011), pp. 601-606

[277]J.A. Inzana, D. Olvera, S.M. Fuller, J.P. Kelly, O.A. Graeve, E.M. Schwarz, *et al.* **3D printing of composite calcium phosphate and collagen scaffolds for bone regeneration** *Biomaterials*, 35 (13) (2014), pp. 4026-4034

[278]F. Tamimi, J. Torres, U. Gbureck, E. Lopez-Cabarcos, D.C. Bassett, M.H. Alkhraisat, *et al.* **Craniofacial vertical bone augmentation: a comparison between 3D printed monolithic monetite blocks and autologous onlay grafts in the rabbit** *Biomaterials*, 30 (31) (2009), pp. 6318-6326

[279]U. Klammert, A. Ignatius, U. Wolfram, T. Reuther, U. Gbureck **In vivo degradation of low temperature calcium and magnesium phosphate ceramics in a heterotopic model** *Acta Biomater.*, 7 (9) (2011), pp. 3469-3475

[280]J. Wang, M. Yang, Y. Zhu, L. Wang, A.P. Tomsia, C. Mao **Phage nanofibers induce vascularized osteogenesis in 3D printed bone scaffolds** *Adv. Mater.*, 26 (29) (2014), pp. 4961-4966

[281]H.W. Kang, S.J. Lee, I.K. Ko, C. Kengla, J.J. Yoo, A. Atala **A 3D bioprinting system to produce human-scale tissue constructs with structural integrity** *Nat. Biotechnol.*, 34 (3) (2016), pp. 312-319

[282]Q. Wang, Q. Xia, Y. Wu, X. Zhang, F. Wen, X. Chen, *et al.* **3D-printed Atsttrin-incorporated alginate/hydroxyapatite scaffold promotes bone defect regeneration with TNF/TNFR signaling involvement** *Adv. Healthcare Mater.*, 4 (11) (2015), pp. 1701-1708

[283]L. Tan, M. Gong, F. Zheng, B. Zhang, K. Yang **Study on compression behavior of porous magnesium used as bone tissue engineering scaffolds** *Biomed. Mater.*, 4 (1) (2009), p. 015016

[284]T.L. Nguyen, M.P. Staiger, G.J. Dias, T.B. Woodfield **A novel manufacturing route for fabrication of topologically-ordered porous magnesium scaffolds** *Adv. Eng. Mater.*, 13 (9) (2011), pp. 872-881