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TISSUE ENGINEERING CONSTRUCTS AND CELL SUBSTRATES

Review Article

Scaffolds and coatings for bone regeneration

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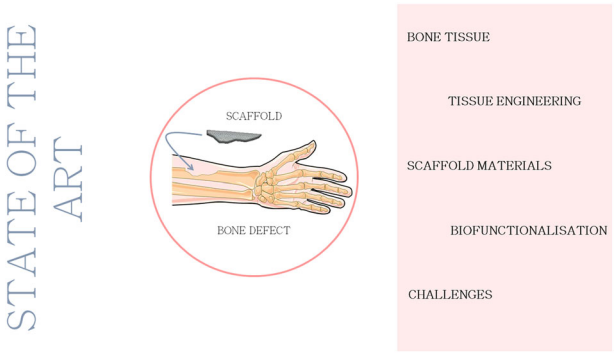
Abstract

Bone tissue has an astonishing self-healing capacity yet only for non-critical size defects (<6 mm) and clinical intervention is needed for critical-size defects and beyond that along with non-union bone fractures and bone defects larger than critical size represent a major healthcare problem. Autografts are, still, being used as preferred to treat large bone defects. Mostly, due to the presence of living differentiated and progenitor cells, its osteogenic, osteoinductive and osteoconductive properties that allow osteogenesis, vascularization, and provide structural support. Bone tissue engineering strategies have been proposed to overcome the limited supply of grafts. Complete and successful bone regeneration can be influenced by several factors namely: the age of the patient, health, gender and is expected that the ideal scaffold for bone regeneration combines factors such as bioactivity and osteoinductivity. The commercially available products have as their main function the replacement of bone. Moreover, scaffolds still present limitations including poor osteointegration and limited vascularization. The introduction of pores in scaffolds are being used to promote the osteointegration as it allows cell and vessel infiltration. Moreover, combinations with growth factors or coatings have been explored as they can improve the osteoconductive and osteoinductive properties of the scaffold. This review focuses on the bone defects treatments and on the research of scaffolds for bone regeneration. Moreover, it summarizes the latest progress in the development of coatings used in bone tissue engineering. Despite the interesting advances which include the development of hybrid scaffolds, there are still important challenges that need to be addressed in order to fasten translation of scaffolds into the clinical scenario. Finally, we must reflect on the main challenges for bone tissue regeneration. There is a need to achieve a proper mechanical properties to bear the load of movements; have a scaffolds with a structure that fit the bone anatomy.

Graphical Abstract



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1 Bone tissue biocomposition

Bone is a complex heterogeneous, hierarchically structured tissue consisting of a mineral phase, hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$); an organic phase (~90% type I collagen, ~5% non-collagenous proteins, ~2% lipids by weight); and contains between 10% and 20% of water [1]. The cellular components of bone consist of osteogenic precursor cells, osteoblasts, osteoclasts, osteocytes, and hematopoietic elements of bone marrow. Osteoblasts are mature, metabolically active and are involved in the bone formation process [2–4]. When osteoblasts are engulfed in mineral, they differentiate into osteocytes. Osteocytes are mature osteoblasts trapped within the bone matrix. From each osteocyte, a network of cytoplasmic processes extends through cylindrical canaliculi to blood vessels and other osteocytes allowing their communication [2, 3]. They are also involved in adaptive remodeling behavior via cell-to-cell interactions in response to the local environment. Osteoclasts are multinucleated which absorbs bone mineral and bone matrix and are controlled by hormonal and cellular mechanisms [2–4]. Bone is highly vascularized and, the blood flow is correlated to its metabolic activity. In long bones, one or two principal diaphyseal nutrient arteries represent the most important supply of blood and pass obliquely through the cortical bone [5, 6].

The bones of the skeleton can provide structural support, allows movement, and provides protection to organs while also regulates mineral homeostasis and blood pH. There are four types of bone based on the shape: long bones, short bones, flat bones, and irregular bones. The long bones are composed of diaphysis; metaphysis and epiphyses. The diaphysis is composed mostly by cortical bone, whereas the metaphysis and epiphysis are composed of trabecular meshwork bone surround by a thin layer of dense cortical bone [7, 8]. There are three types of bone based on their anatomical shape and composition: woven bone, cortical bone, and cancellous bone. Woven bone is found during embryonic development, during fracture healing (callus formation), and in some pathologic states such as hyperparathyroidism and Paget's disease. Cortical bone is dense and solid and surrounds the marrow space, whereas trabecular bone is composed of a honeycomb-like network of trabecular plates and rods interspersed in the bone marrow compartment [3, 7]. At the macrostructure level, bone can be distinguished into: trabecular (corresponding to around 20% of the total skeleton), which forms a solid osseous shell around the bone and consists of dense and parallel, concentric, lamellar units—the osteons; and cortical bone (corresponding to around 80% of the total skeleton) which is remodeled from woven bone. The trabecular bone is supplied by diffusion from the surrounding bone marrow and it is surrounded by cortical bone but the thickness and strength of the cortical shell depend on location [3, 9–11]. Although both types of bone are easily distinguished by their degree of porosity (trabecular bone is much more porous) they have other differences such as trabecular bone being more metabolically active [3, 10].

2 Bone healing process

Mechanical properties of bone depend on age, anatomical site, and gender. The elastic modulus is the biomechanical property of bone that draws more interest because of its critical importance for characterizing bone pathologies and guiding bone scaffolds design [10, 12]. Mechanical stimulation has a major influence on bone biomechanics properties. According to Wolff's law, the mechanical loading stimulates bone formation [13]. Bone's viscoelasticity is a crucial property when referring to bone fracture. The viscoelasticity and the strength of bone are properties that are intimately related to its porosity [14].

Following a bone lesion, the principal factors that influence the process of bone healing are the availability of blood supply, the mechanical stability, the size of the defect, the incidence and severity of surrounding tissue injuries [15]. The process of fracture healing can be considered a regenerative process and it is a complex biological process. Bone heals by either direct or indirect fracture healing. The most common process is indirect fracture healing and occurs in three overlapping stages: the early inflammatory stage, the repair stage, and the late remodeling stage [3]. In the inflammatory stage, a hematoma develops within the fracture site during the first few hours and days. Inflammatory cells (macrophages, monocytes, lymphocytes, and polymorphonuclear cells) and fibroblasts infiltrate the bone under prostaglandin mediation. This results in the formation of granulation tissue, ingrowth of vascular tissue and migration of mesenchymal cells. As vascular ingrowth progresses, a collagen matrix is laid down while osteoid is secreted and subsequently mineralized, which leads to the formation of a soft callus around the repair site. Eventually, the callus ossifies by the deposition of osteoblasts forming a bridge of woven bone between the fracture fragments [3, 16, 17]. Once the fracture has been satisfactorily bridged by callus, the newly formed bone is restored to its original shape, structure, and mechanical strength. Any excess callus is removed and the woven bone is remodeled into the trabecular bone. The fracture healing is completed during this stage—the remodeling stage. Direct healing is not a natural process. It requires an anatomical reduction of the fracture ends and a stable fixation when these requirements are achieved the direct bone healing can occur [18]. Bone healing is a major complex process that requires the recruitment of mesenchymal stem cells (MSCs) and once

they are recruited, a molecular cascade starts involving collagen type I and collagen type II matrix production and the participation of several peptide-signaling molecules. Growth factor-beta (TGF-β) superfamily members such as TGF-β2, -β3 and growth differentiation factor 5 (GDF-5) are also involved in the healing process. Bone morphogenetic protein (BMP-2), vascular endothelial growth factor (VEGF) and the involvement of the actions of metalloproteinase are key factors for the healing cascade [18]. There are numerous biochemical and cellular factors related to the bone healing that associated with a biomechanical and anatomical process, complete an appropriate regeneration of bone defects.

3 Treatments for bone lesions

To fully understand bone regeneration is important to define some concepts that are closely related. Osteogenesis, osteoinduction, osteoconduction, and osteointegration are the four essential characteristics for the success of the scaffold. Osteogenesis is the capacity to produce new bone by the differentiation of osteoblasts. Osteoinduction has been defined as the process of recruitment, proliferation, and differentiation of host mesenchymal stem cells into chondrocytes and osteoblasts. Osteoconduction is the ability to provide an environment capable of hosting the indigenous mesenchymal stem cells, osteoblasts, and osteoclasts. The final bonding between the host bone and the scaffold is called osteointegration [19, 20].

There are numerous approaches to promoting bone tissue regeneration. One of the possible treatment is a surgical procedure with autograft or allograft bone [21, 22]. Autologous bone grafts consist of taking bone from another part of the patient's own body and is considered the clinical "gold standard". It is the most effective method for bone regeneration as it promotes bone formation over its surface by direct bone bonding and induces local stem cells to differentiate into bone cells without any associated immune response. It is commonly taken in the form of trabecular bone from the patient's iliac crest. Although it presents a relatively good degree of success, the range of cases in which it can be used is restricted, mainly due to the limited amount of the autograft that can be obtained and due to donor site morbidity [11, 23]. The vascularized free fibular bone graft is a type of autogenous bone graft and it was first described in 1975 by Taylor [24]. It is used in large bone defects, more than 5–6 cm [25]. The advantage of this method is the availability of bone stock, a faster union, less resorption of bone and lower fatigue fracture. This process involves a long surgical procedure and can increase the morbidity on the donor site. In addition, there is a demand for further information about the factors that lead to failure [25, 26].

Allograft, bone is taken from a donor, could be an alternative to the use of autografts. However, when compared with autograft the rate of graft incorporation within the bone is lower. Allograft likewise may cause immune rejection and pathogen transmission from donor to recipient, and although infrequent, infections could occur in the recipient's body after the transplantation [11, 27]. In 1957 bovine bone was first introduced [28]. Xenograft bone substitutes have their origin from a species other than human, it is similar to autologous bone grafts in that both are osteoconductive and relatively inexpensive [29]. However, there may be a transmission of animal diseases.

Recently, the induced membrane technique or Masquelet technique has been used to treat large bone defects. It is a two-step procedure: first, radical soft tissue and bone debridement are undertaken, then a cement spacer of polymethyl methacrylate (PMMA) is placed at the site of the bone defect and is stabilized with an external fixator [30, 31]. The cement spacer prevents fibrous tissue invasion of the defect and induces the surrounding membrane hat will promote the revascularization of the bone graft [32, 33]. Secondly, 6–8 weeks later the induced membrane is carefully incised, the spacer removed and cancellous bone from the iliac crest is implanted and the membrane closed with definitive fixation. Although is an interesting method, there are complications and studies for a better understanding of the procedure and complications are necessary [34].

4 Scaffolds for regeneration

4.1 Scaffolds-based tissue engineering

Tissue engineering paradigm has several components: a scaffold that mimics the tissue that needs to be regenerated; cells to lay down the ECM; morphogenic signs so cells can differentiate. Tissue engineering can be applied to all types of tissues that constitutes human body such as bone tissue [35, 36], osteochondral [37, 38], cartilage [39, 40], neural tissue [41, 42]; skeletal tissue [43, 44]; skin [45, 46]; meniscus [47, 48]; or even blood vessels [49]. Bone tissue engineering strategies aim to achieve bone regeneration which is required in several clinical conditions including but not limited to osteoporosis [15, 50], bone infection [15] and resection of musculoskeletal sarcoma which usually results in large bone defects [51].

Tissue engineering products for bone treatment can be divided into two groups: those that stimulate bone regeneration and those that provide a permanent solution, as a substitute for bone [52]. For the treatment of bone defects, the ideal scaffold should be developed to meet some important requirements (Table 1).

Table 1 Requirements for the design of scaffolds in bone tissue engineering [12, 136, 153, 154]

Features for the success of scaffold	Importance of the feature
Biocompatibility	Capacity to be in a host tissue without initiate an inflammatory response
Osteoinductive	Able to recruit and differentiate mesenchymal cells
Chemistry	Influence cell behavior
Suitable surface topography	Influence cellular behavior such as adhesion, proliferation, and differentiation
3D structure	Host of the newly formed tissue Allows the formation of new tissue in a 3D manner
Mechanical properties	Support the defect area Influence cell behavior
Porosity and pore shape	Allows tissue ingrowth, nutrient and oxygen change; neovascularization and influence cell behavior
Wettability	A proper wettability enhances the adhesion of proteins and thus the cell attachment

Studies that compare the bone regeneration using autograft with materials that can be used as substitutes have been performed. Bioactive glass (BG) is an interesting biomaterial especially due to its ability to form a reactive carbonated HA layer [53]. A prospective randomized study was performed in 25 patients with benign bone tumors. The patients were surgically treated with either bioactive glass S53P4 (BG) or autogenous bone (AB) as bone graft material. It was observed a significant difference was presented between the AB and BGs group in how the bone cavities remodeled over time. The time of disappearance was significantly longer in the BG. For a more reliable conclusion, the study should have a longer period of patient analysis [54].

Calcium phosphate types of cement have been developed in order to be injected as a doughy substance and that cancan cure over several hours upon implantation. In 1998, the first injectable biologic cement was approved by the Food and Drug Administration (FDA). Injectable mineral types of cement are widely used as a solution to treat bone defects due to their chemical composition being close to the mineral component of bone ECM. They have an advantage over blocks, granules, and pellets, in that a personalized fill of the defect is possible [19]. In a retrospective chart review, a direct comparison of autografts, bone cement, and demineralized bone matrix in terms of function and outcomes was performed. Demineralized bone matrix was the primary reconstructive material used in six patients. Seventeen patients had bone cement as the reconstructive material for cranioplasty; six patients had demineralized bone matrix, and five patients had bone autografts. It was concluded that residual defects and revision rates were significantly less when autograft or bone cement was used [55].

An injectable composite cement of phytic acid-derived bioactive glass with a high content of BG was recently developed and tested in vivo in a rabbit femoral condyle defect. The outcomes revealed that the cement had a better capacity than the polymethyl methacrylate and calcium sulfate cement in terms of bone regeneration as well as the resorption rate observed in a critical-sized rabbit femoral condyle defect model. This made this cement promising for the treatment of bone defects as at the 12th week, showed signals appeared at the edge of the implanted cement, indicating new bone [56]. A large number of bone-graft alternatives are currently commercially available for orthopedic use. They vary in composition, mechanism of action and characteristics. Their composition includes mineral composites, ceramics, mineral cement, BGs and synthetic bone substitutes [19, 57]. Table 2 summarizes the current commercially available products for treating bone lesions. An important observation on what is being commercialized is that most of these products' purpose is to fill the defect and not to promote bone regeneration. It is expected from the next generation of products to be multifunctional by incorporation of growth factors and/or cells.

The biomaterial biocompatibility can be evaluated. In the design of tissue engineering scaffolds parameters including surface topography, chemistry, surface energy, and wettability, pore size, shape, mechanical properties should be optimized to maximize the bone ingrowth [58, 59]. Moreover, elasticity, compression or shear stress can influence cell behavior and even epigenetic status [60, 61]. Surface characteristics are critical for the successful design and medical application of biomaterials as the surface is the earliest contact with the biological environment [8, 62].

Surface properties, both chemical and topographical, can influence cellular adhesion and proliferation as it is involved in many of biological events occurring after implantation, which range from protein adhesion to bone remodeling [11, 63]. Topographies such as random nanofibers normally can influence cells into spreading and polygonal shapes which promote the process of osteogenic differentiation [64].

Table 2 Commercially available products used to treat bone lesions

Composition	Form	Product	Company	Reference
Calcium phosphate	Paste	Norian SRS	Synthes (PA, USA)	[57, 155]
50% calcium sulfate, 10% calcium phosphate, and 40% DBM	Paste	PRO-STIM	Wright Medical Technology (TN, USA)	[156]
A mix of calcium hydroxide and iodoform	Paste	Vitapex	Neo Dental Chemical Products (Tokyo, Japan)	[157]
Silicate substitute calcium phosphate	Paste	Infuse	Medtronic (Minneapolis, USA)	[158, 159]
19.5% demineralized bone, 12.5% cancellous allograft and reverse phase medium (RPM)	Putty or paste	OrthoBlast	Isotis Orthobiologics (CA, USA)	[160]
Porous silicon substituted HA granules	Paste/solid	ACTIFUSE	Baxter International (IL, USA)	[158, 161]
DBM/gelatin	Gel/paste/solid	Optefil	Exactech (FL, USA)	[162, 163]
Calcium sulfate and DBM	Putty	Allomatrix	Wright Medical Technology (TN, USA)	[164, 165]
Dibasic calcium phosphate and collagen type I	Solid	CopiOs	Zimmer (IN, USA)	[166]
Porous hydroxyapatite granules + porous porcine gelatin-based foam matrix	Solid	nanOss Bioactive 3D	Pioneer Surgical Technology (MI, USA)	[167]
Porous β-TCP combined with bovine collagen type I	Blocks/foams strip/morsels	Vitoss	Orthovita (PA, USA)	[168, 169]

Many studies have shown a relationship between cell attachment and surface roughness. In a study, three variations of surface-modified porous titanium and conclude that the surface treatment improved cell response [65]. It was observed in a study [66] that cells exhibit protruding filopodia in honeycomb-like scaffolds of PCL/nHA which indicates a proper cell spread. For achieving the adequate scaffold integration, a surface with roughness is favorable as it cancan enhance attachment, proliferation, and differentiation of anchorage-dependent bone-forming cells [62, 63, 67, 68]. Parameters such as wettability and surface free energy can also influence cell growth as it was observed in a study [69]. It was concluded that surface free energy was a critical parameter for cellular adhesion and proliferation rather than roughness.

The importance of having a porous scaffold in bone regeneration was shown a study where a porous scaffold of hydroxyapatite (HA) for BMP-2 delivery was tested using a rat model [70]. In order to achieve a solid bone regeneration in a scaffold, it is necessary a proper vascularization. Moreover, cells from the surrounding must be able to penetrate. Pore size is, thus, an important feature since if the pores are too small, pore occlusion by the cells will happen and it is also an important factor for protein adsorption, cellular migration and osteoconduction [11, 71]. Pore sizes greater than 300 µm are recommended for bone ingrowth in comparison with smaller pore size [67, 72–74]. Fukuda et al. [75] compared the osteoinduction for different pore sizes, 500 µm, 600 µm, 900 µm, and 1200 µm, in identical environments. In this study, a 500 µm pore size presented excellent osteoinduction. However, in another study with different pore sizes [76] including 300 µm, 600 µm, and 900 µm, it was observed significantly higher fixation ability in 600 µm pore size. An experiment with scaffolds with pore sizes of 60 µm, 100 µm, 200 µm, and 600 µm was performed by Prananingrum et al. [71] after three weeks implanted into rabbit calvaria the scaffold with 600 µm pore size showed a greater bone ingrowth. Nevertheless, after 20 weeks the pore size of 100 µm presented greater bone ingrowth than the other pore sizes. In that study, they suggested that bone regeneration into porous scaffolds is pore size-dependent whereas bone ingrowth was most prominent for the 100 µm sized pores after 20 weeks in vivo. Porosity and pore size of a scaffold for bone tissue regeneration are key factors that will improve biologically allowing bone ingrowth and infiltration of cells and nutrients. Nevertheless, these features become conflicting with others as the increase of pore size the strength of the scaffold decrease which can lead to failure in vivo.

Today, biomaterials that are used to prepare scaffolds can be natural or synthetic, degradable or non-degradable. For example, natural polymers chitin and chitosan or collagen are being used for applications in tissue engineering [77, 78]. Synthetic polymers such as Polycaprolactone (PCL), Poly-lactic acid (PLA) or Poly (lactic-co-glycolic) acid (PLGA) are biodegradable and can be produced with different features for applications in bone tissue engineering [79]. Table 3 overviews the advantages and disadvantages of the most common materials used in the bone. Among those, hydrogels possessing hydrated polymer chains have been gaining much attention as a delivery system of cells and growth factors for bone tissue engineering applications [80, 81].

Table 3 Advantages and disadvantages of the most common bone substitutes [154, 170, 171]

Biomaterial	Advantages	Disadvantages
Autologous	Osteoinductive Non-allogenic Osteogenic Osteoinductive	Limited availability Donor site morbidity Inadequate vascularization Unpredictable resorption Donor site pain
Allograft	No donor site morbidity High availability Osteoconductive Osteoinductive	Limited osteogenicity Delayed incorporation Inadequate vascularization Low availability of healthy grafts Rejection of the graft Risk of disease transmission Re-injury Ethical concerns
Xenograft	More economic No donor site morbidity/ pain High availability Osteoconductive Osteoinductive	Limited osteogenicity Delayed incorporation Inadequate vascularization Availability of healthy grafts Rejection of the graft more aggressively Risk of zoonotic disease transmission Re-injury Ethical concerns
Metals	Excellent mechanical properties Biocompatible Osteointegration Personalized manufacturing	Corroding risk Risk of toxicity of metal ions Inadequate vascularization Bioinert
Ceramics	Biocompatible Personalized manufacturing Good mechanical properties Excellent resistance to corrosion	Brittle Low elasticity Inadequate vascularization
Polymers	Biocompatible Personalized manufacturing Good mechanical properties Low young modulus	Inadequate vascularization

4.2 Metallic biomaterials

Biodegradable metals like Mg, Zn, Fe, and their alloys have a potential for load-bearing application and they are used in clinics for more than a decade [82, 83]. The first use of Fe to repair the human body was as a dental implant [84]. Recently, the potential of biodegradable Mg screws was evaluated for the fixation of vascularized bone graft in osteonecrosis of the femoral head patients. The of this study results suggested that the treatment efficacy in terms of better stabilization of the bone flap as compared with the conventional [85].

Metallic non-degradable biomaterials are mainly used for the fabrication of scaffolds for the replacement of hard tissue such as artificial hip joints, bone plates, and dental implants. These are attracting a great deal of attention due to their mechanical properties and corrosion resistance [86–88]. Stainless steel was the first metallic biomaterial used successfully as an implant and it is one of the main metallic materials used amongst with Co-based alloys, Ti and its alloys [87, 89, 90]. Stainless steel is a popular metal for use as an acceptable cup (one half of an artificial hip joint) applications [88, 91]. Stainless steel materials are resistant to a wide range of corrosive agents due to their high Cr (Chromium) content which cancan allow the formation of the strongly adherent, self-healing and corrosion resistant coating oxide.

Titanium and its alloys are widely used in biomedical applications due to their excellent mechanical, physical, biological performance, corrosion resistance, and their outstanding biocompatibility. Commercially pure Ti (CP Ti), typically with single-phase alpha microstructure, is currently used in dental implants while titanium with 6% aluminum and 4% vanadium, Ti6Al4V, is mostly used in the orthopedic field. The Al and V alloy elements stabilize the alpha-beta microstructure and improve the mechanical properties [92, 93]. The Ti6Al4V is used for their excellent corrosion resistance and their modulus of elasticity (113 GPa) that is approximately one-half that of stainless steel (210 GPa) and Co–Cr alloys (240 GPa) and consequently the stress shielding will be lower [93–96].

Ti-mesh as an alternative treatment for the reconstruction of critical segmental bone defects was tested [97]. They observed bone formation on the scaffold surface in a case example of a 61-year-old woman with non-union of the femur 16 months after an initial fracture treatment. However, there was no radiographical evidence of bone growth through the scaffold mesh. Moreover, not all cases showed reliable bone defect bridging. In this study, they also investigate bone regeneration within the mechanobiological optimized scaffolds in 27 adult sheep. A soft or a stiff scaffold, filled with the autologous cancellous bone graft (ABG) was applied within the defect and stabilized with either common steel locking compression plate (LCP) or a rigid, custom-made shielding plate. Four groups were tested: soft + LCP; stiff + LCP; soft + shielding plate and stiff + shielding plate. It was observed by the radiographic follow-up that the soft and stiff scaffolds in combination with the locking compression plate showed bone formation

patterns similar to those observed in clinical cases. They observe that a relatively soft, mechanically optimized Ti-mesh scaffold filled with ABG enhanced regeneration in a large segmental bone defect in sheep. Machined (MTi) and alumina-blasted (ABTi) titanium discs were combined with adipose-derived stem cells (ASCs) to be tested in female sheep [98]. There was no statistically significant difference in the formation of new bone generated. This could be due to the necessity of a longer period of the experiment.

4.3 Ceramic biomaterials

Ceramics are generally defined as inorganic, non-metallic materials [99]. Bioinert ceramics such as Al, Zr, and several porous ceramics are the most used in orthopedic devices [92, 100]. Alumina has a great performance under compression, but is brittle under tension and has been used for nearly 20 years owing to its low friction and wear coefficients [92, 100].

Calcium phosphate ceramics have been widely used as bone substitutes, coatings, types of cement, drug delivery systems, and tissue engineering scaffolds [101]. Tricalcium phosphate (TCP) $Ca_3(PO_4)_2$ is a bioactive and biodegradable ceramic material. TCP implants have been used for two decades as the synthetic bone void fillers in the orthopedic and dental application, as it can be observed in Table 2 the majority of commercial products are composed by calcium phosphates. BG and its related glass-ceramic biomaterials are an interesting biodegradable biomaterial used in scaffolds for bone regeneration [102]. BG was also used to reinforce gellan-gum spongy-like hydrogel [53].

Zirconia is one of the ceramic materials with the highest strength suitable for implants and presents other advantages like being bioinert, having excellent resistance to corrosion and wear, high fracture toughness and one of the most is biocompatible [92, 103, 104]. These favorable mechanical properties are a consequence of phase transformation toughening, which increases its crack propagation resistance [99, 105].

4.4 Polymer biomaterials

Biodegradable polymers can be classified into two types: natural polymers and synthetic polymers. Synthetic polymers have been widely studied especially polyglycolic acid (PGA), polylactic acid (PLA), polylactide-co-glycolide (PLGA), poly (d,l-lactic acid), polyethylene glycol (PEG), and PCL [106]. PGA is very similar to PLA however PLA exhibits different chemical, physical, and mechanical properties because of the presence of a pendant methyl group on the alpha carbon [107]. These polymers can be used as a drug delivery system [108]. Although they present characteristics like having good processability and manageability they lack rigidity and stability [109].

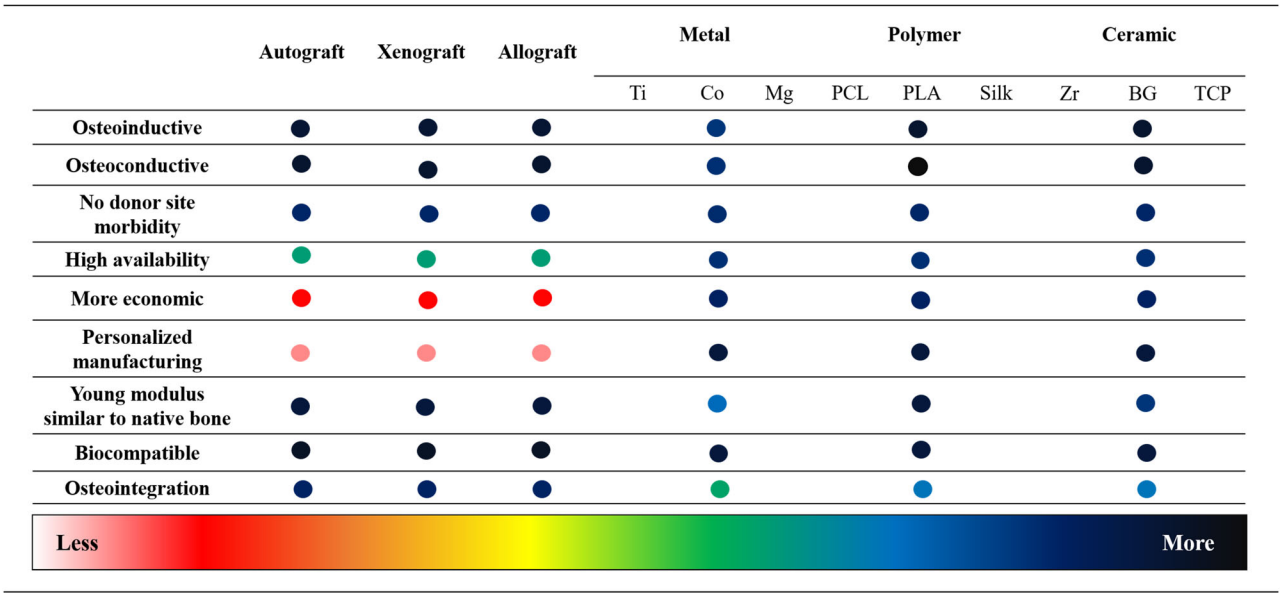
Alenezi [110] studied PLGA microspheres within β-TCP for bone regeneration using a rabbit's calvaria defect model. They showed that PLGA was capable of releasing clarithromycin increasing the bone regeneration. Natural polymers usually contain specific molecular domains that can support and guide cells and thus enhance the biological interaction of the scaffolds with the host tissue [111].

Collagen is the major component of the animal connective tissue and due to its properties has been widely investigated for biomedical applications. Materials based in collagen are suitable for both cartilage and bone scaffolds. Scaffolds composed by: collagen (fibrillar collagen type I, III, and V from bovine tissue)/hydroxyapatite/β-tricalcium (CHT) phosphate; CHT plus growth factor cocktail (GFC); a jellyfish collagen (Rhopilema sp.) matrix; jellyfish collagen (Rhopilema sp.) matrix plus GFC; a collagen powder (fibrillary collagen type I, III, and V from bovine tissue); a collagen powder and a collagen powder (fibrillary collagen type I, III, and V from bovine tissue) plus periodontal ligament stem cells PDLSC were compared in terms of bone growth in lower jaw of mini pigs. No additional significant enhancement of bone growth was observed upon the use of GFC or PDLSC [112].

Silk is a natural fibrous polymer consisting of repetitive protein sequences and due to its characteristics such as elasticity, biocompatibility and biodegradability have applicability for bone regeneration [113–115]. Three different scaffolds: alginate, alginate/hydroxyapatite, and alginate/hydroxyapatite/silk fibroin were analyzed in an experiment [115]. Central calvarial bone defects of forty Sprague Dawley rats were grafted with alginate, alginate/hydroxyapatite, or alginate/hydroxyapatite/silk fibroin. Four weeks after implantation the bone formation was evaluated, it was observed higher bone formation when the composite alginate/hydroxyapatite/silk fibroin. Silk and hydroxyapatite co-operated in a study [116]. The new bone formation was evaluated for 12 weeks and it was observed higher bone formation in hydroxyapatite-conjugated silk fibrin scaffold group. In spite of numerous in vitro and in vivo studies, there are still no silk based scaffolds in human trials [117].

Alginate is a polysaccharide that has been widely used in bone tissue engineering. The main application of this biomaterial is as the delivery vehicle was reported in a recent study where an alginate system was modified to enhance its cell adhesion, and osteogenic and proangiogenic properties using gum tragacanth [118]. Alginate also has the potential to induce osteochondral regeneration. In a study, it was tested biphasic alginate in six adult sheep and rabbits. Although, it was shown bone substitution a comparison with the commercially available product is needed [119].

Table 4 Comparison of the different solution for bone defect treatment



Chitosan is a polysaccharide that can be used in many applications. It exhibits antibacterial activity, along with antifungal, mucoadhesive, analgesic and hemostatic properties [120]. A composite scaffold consisting of chitosan (CS), gelatin (Gel) and platelet gel (PG) was studied [121] in terms of its healing potential. They observed that their scaffold showed significantly higher new bone formation, the density of osseous and cartilaginous tissues, bone volume, and mechanical performance. It is well accepted that biodegradable polymers are a great biomaterial for bone applications, however, they present problems such as: the relationship between degradation rate and mechanical properties; there is poor degradation rate control; there is a mismatch between the polymeric biomaterial and the bone. The synthetic polymers also present some cons as they have poor cell adhesion and lack of bioactivity; their degradation products are acidic which can cause inflammation [122].

PEEK is biocompatible, chemically and physically stable, with excellent mechanical properties and it can be processed using a variety commercially techniques [123, 124]. Moreover, PEEK is stable at high temperatures with a high melting point of 334 °C, is insoluble in all conventional solvents at room temperature, with exception of 98% sulfuric acid and it remains stable in sterilization processes [123–125]. The major beneficial property for orthopedics application its lower Young's (elastic) modulus (3–4 GPa) being close to the human bone (17.7 GPa) in comparison with Ti alloy (113 GPa) and Co–Cr alloy (240 GPa) which reduces the stress shielding after implantation [125–127]. The bioactivity of porous PEEK was studied. [128] using nine rabbits. Their findings suggest that the surface modification of PEEK may improve cell-material interaction. At 4 weeks post-surgery, an impermeable structure was observed in both groups however, the bone tissue could not be observed in the bare PEEK group. In Table 4 is possible to have a general comparison of the different solutions already discuss in this review.

Regardless of notable progress in bone tissue engineering relatively few orthopedic designed have been used in clinical [15]. The main limitation regarding current approaches is insufficient vascularization and poor nutrient transport in the scaffold resulting in the death of cells which leads to a reduced osteointegration. Another limitation and although there is a great demand in producing porous scaffolds is the mechanical strength as it is heavily dependent on porosity and geometry of the scaffold. Therefore the big challenge in producing scaffolds for bone regeneration is in developing an approach that allows cell penetration, nutrient, and oxygen exchange and still is able to support load [15, 129].

In vitro assays allow the understanding of the fundamental biological mechanism, the biological activity, toxicity and also the evaluation of the cell response to the biomaterial. In this sense, animal models are crucial in providing complementary information on biological reactions such as inflammatory reactions between scaffolds and bone and even to evaluate the performance of the scaffold. a number of animal models, such as rat/mouse, rabbit, sheep, goat, and pig have been used to simulate human environment [130, 131]. Table 5 represents the recent in vivo studies performed to test scaffolding biomaterials for bone tissue applications.

5 Biodegradable coatings for scaffolds

Each biomaterial has its own advantages and disadvantages as bone scaffold biomaterial which could be overcome by combining different biomaterials. To improve the properties of scaffolds for bone tissue applications, taking advantage of the good mechanical properties of some materials and the bioactivity of other, researchers have been coating them with materials that mimic the natural bone surface [132, 133]. There are key requirements for coated products such as adequate stability of the coat in the biologic agent in excipient coating matrix; optimized kinetics; ability to be sterilized by conventional techniques [134].

A study performed in 1988 [135] used plasma-spray to coated titanium implants with apatite and evaluated in vivo in a canine model. The authors reported that apatite-coated implants could bond as strong as the cortical bone itself. Calcium phosphate-based materials such as HA, β-TCP and biphasic calcium phosphate have a similar composition of natural bone which allows them to directly bond to living bone [136, 137]. HA ($Ca_5(PO_4)_3(OH)$) is important calcium phosphate since its chemical composition and structure are very similar to the mineral component of natural bone. It has exceptional characteristics such as bioactivity, biocompatibility and can achieve very high mechanical strength. As a coating, it can provide to the scaffold osteoconductivity that enhance the cell attachments and proliferation [29, 138, 139]. β-TCP is a well-characterized osteoconductive biomaterial that can be used for bone regeneration applications.

In 1971, Hench et al. discovered that BG, a silicate glass-based, was able to bond with the bone and soft tissues [140]. 45S5 and 13–93 are two well-known bioactive glasses. This material has an amazing ability to form an interfacial bond with the host tissue; when implanted, they induce the formation of a dense surface layer of hydroxycarbonate apatite (HCA), which is very similar to the mineral component of bones and ensures a great adhesion. BG is a silicate based and by varying the proportions of sodium oxide, calcium oxide, and silicon dioxide, all range of forms can be produced from soluble to non-resorbable. They possess both osteointegrative and osteoconductive properties [57, 136]. One limitation of the use of 45S5 glass and other bioactive glasses is that the local biological microenvironment is influenced by their degradation products [136]. Borate bioactive glasses presents properties that allow cell proliferation and differentiation in vitro [141]. In a study, where it was compared to the ability to repair bone defects of both β-TCP and BG and conclude that BG had better performance, [142]. They also observed that the dissolution products of BG were capable of promoting osteogenesis which can lead to the regeneration of the bone defect. Although BG has good potential for regenerate bone the concentration of boron released is still a concern. A similar conclusion was reached in another study [143]. In this study, it was developed and tested a 3D porous structure of Ti6Al4V coated with BG. The in vitro results demonstrated cell attachment, proliferation, and differentiation of human bone marrow stromal cells. The obtained coating presented stability and interfacial adhesion.

Polysaccharide based tissue engineered periosteum composed of heparin-coated chitosan nanofibers was studied in terms of delivering growth factors, support adipose-derived mesenchymal stem cells (ASCs) delivery and improvement of the incorporation of the allograft in a critical-sized mouse femoral defect [144]. Female mouse received untreated allografts, allografts seeded with ASCs, allografts modified with nanofibers, or allografts modified with nanofibers and ASCs. They observed that the ASCs were delivered, also FGF-2 and TGF-β1 were delivered successfully. It was observed, after 6 weeks of implantation, a non-significant increase in the bone callus volume.

There are various techniques to coat scaffold's surface such as: spin coating, which is one of the most popular technique to obtain uniformly thin coatings [145]; sol–gel process is being used to prepared bioactive glasses [146]; electrophoretic deposition (EPD) is gaining attention in the biomedical field as it can achieve uniform coating in scaffolds with complex and porous shapes [147]; auto-catalytic deposition [148]; dip coating [149]; spray deposition [150, 151]; ion beam assisted deposition [152] and other techniques.

Although the coatings studies were translated into thousands of publications very few products have accomplished clinical implementation. It is crucial for scaffold's good performance its surface properties. The functionalization of the scaffold's surface with bioactive coatings is a promising strategy, yet it presents limitations such as the difficulty of achieving and uniform coat and interfacial adhesion.

6 Conclusions and final remarks

The regeneration of bone defects is a complex problem. Although there are numerous studies applying bone tissue engineering to regenerate bone defects there still no optimized approach due to high rates of complication and poor functional outcomes. Several products have been proposed like the use of coatings with a similar composition of the bone to overcome the lack of osteointegration. However, coatings need to present sufficient mechanical integrity and surface adhesion to support the mechanical load. In order to allow cell and vessels penetration for a proper bone formation porous scaffolds have been proposed. Nevertheless, the introduction of pores may lead to a decrease in

Table 5 Scaffolding biomaterials used in the recent in vivo experiment for bone tissue engineering studies, and the outcomes

Biomaterial	Cells	Growth factors	Animal model	Follow up	Reported outcome	Ref.
Titanium + gelatin	–	VEGF; TGF-ß1; TGF-ß2	Rabbit	8 weeks	Two months after the surgery, mature bone tissue nearly filled in the hole of the treated group. While more soft tissue and new bone were observed in the holes of the control group.	[172]
Ti6Al4V coated hydroxyapatite	–	–	Rabbits	12 weeks	Osteointegration and osteogenesis observed. However, the study did not perform a control group.	[173]
Titanium	–	–	Pigs	5 weeks	Porous titanium, PEEK, and allograft pins were press-fit into pig's skull and results were compared. Osteointegration of the titanium scaffold was observed.	[174]
Ti6Al4V	–	–	Rabbit	10 weeks	Both solid and porous implants were osseointegrated, however, the porous implants allowed more bone growth. A con of this study was the absence of a control group.	[175]
Ti6Al4V	–	–	Goats	12 months	At 12 months was observed new bone formation at both ends and in the middle of scaffold. This study did not have a control group for the in vivo tests.	[176]
PEEK	–	–	Rat	12 weeks	Bone ingrowth into the pore network was observed. However, the study did not perform a control group.	[177]
PEEK	–	–	Rabbit	12 weeks	Adjacent tissue integration and bone ingrowth were observed. The study did not perform a control group.	[128]
HA/alumina	–	–	Dog	8 weeks	New bone formation in the defect. The study lacks group control.	[178]
β-tricalcium phosphate	BMSCs	–	Non-Human Primate femur	15 months	Five of seven cases showed the bone union of the defect. In the group, without BMSCs four of five failed the regeneration.	[179]
β-tricalcium phosphate + platelet-rich fibrin	–	–	Pig	12 weeks	This study aimed to evaluate the effect of PRF alone and combined with β-TCP. They observed more new bone formation with the combination of PRF and β-TCP.	[180]
Poly (L-Lactic- acid)-poly (ε-caprolactone)	SSCs	–	Sheep	12 weeks	The analyses confirmed a trend towards increasing bone formation, however, this study had a small number of animals studied (n = 4).	[181]
Poly (glycerol sebacate)	Blood cells	–	Rabbits	8 weeks	The ulna critical defect was fully regenerated in 8 weeks. However, this study had a small number of animals studied (n = 5) and did not have a group control.	[182]
Collagen type I/hydroxyapatite	MSCs	–	Rabbits	12 weeks	Improved the biomechanical properties of a Coll/HA Scaffold, bone regeneration was observed.	[183]
β-tricalcium phosphate coated with polylactic co glycolic acid	MSCs and EPCs	VEGF	Dog	8 weeks	The bone formation was better in scaffolds containing MSC, either mixed with EPC or incorporating VEGF. In this study, it can also be concluded that there is no benefit in adding both EPC and VEGF.	[184]
Hydroxyapatite/magnetite	–	–	Rabbit	12 weeks	Both hydroxyapatite/magnetite and pure hydroxyapatite present similar biomechanical properties. In terms of osteogenic behavior, the commercial hydroxyapatite scaffolds exhibited similar results as the magnetic porous hydroxyapatite scaffolds. It was observed ate 4^{th} week bone formation.	[185]

Table 5 (continued)

Biomaterial	Cells	Growth factors	Animal model	Follow up	Reported outcome	Ref.
Magnesium/hydroxyapatite	–	RhBMP-2	Goat	12 weeks	This study concluded the importance of magnesium in bone formation and angiogenesis. It was shown that both Magnesium/Hydroxyapatite and Magnesium/Hydroxyapatite/rhBMP-2 promote bone regeneration.	[186]
Bioactive glass/gelatin	MSCs	BMP-7	Rats	12 weeks	The combination of bioactive glass/gelatin/MSCs-BM was proven to be effective in the promotion of bone regeneration. After 12 weeks of implantation, it was observed newly formed bone.	[187]
PLGA-PEG-PLGA	–	VEGF PDGF BMP-2	Ovine	6 months	This study allowed concluding that the inclusion of VEGF and PDGF had no effect on bone regeneration. On the other hand, the regions with VEGF And PDGF increased the vascularization.	[188]

mechanical properties. Growth factor delivery treatment presents successful results in many studies but there have been growing issues caused by the use of certain growth factors, proper dosage, and combination. It is important to optimize the scaffolds so they can match the mechanical characteristic of bone. The majority of the strategies were only tested in small animal models such as mice and also testing in large animal models is important to properly analyze the effects. Current scaffolds are not chemically or patient-specific which makes them not ideal for many clinical applications. This is a tremendous gap that should be overcome in order to fasten their translation into clinics. A great challenge is the production of a biomaterials scaffold that replicates the highly porous structure of cancellous bone while having high mechanical strength to provide support in load-bearing defects.

In summary, the main challenges for bone regeneration are to achieve proper mechanical properties to bear the load of normal movements; have a scaffolds that allows vascularization in order to obtain a fully mature bone, moreover, the scaffold has to be heterogeneous as bone is not uniform biologically and biomechanically; lastly the use of the scaffolds should be easy to handle and a one-step procedure.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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