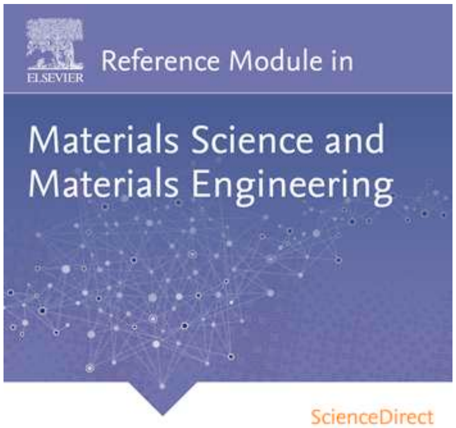

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Biomaterials for Bone Replacements: Past and Present

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1 Introduction

Bone damages and imperfections indicate a noteworthy medical issue. An assortment of techniques, such as alloplastic, allografts and auto grafts materials are utilized to treat absconds. Be that as it may, bone tissue engineering gives an elective system to the fix of bone deformities [1,2]. Metal is a typical materials utilized in the biomedical field for implants. Its high tensile strength and fatigue characteristic make it reasonable for a variety of uses, for example, dental implants, and joints, for example, knees and hips. Nevertheless, metals have restrictions identified with consumption, which can prompt to toxicity or hypersensitivity responses [3]. Over the last five decades, all classes of materials including metallic, ceramic, polymeric and composite have drawn engineers and scientists for biomedical applications [4,5]. Current advancements with biomaterial innovation are presently converting into the development of a third-generation of biomaterials that can invigorate a particular cell reaction [6]. Nowadays, the synthetic biomaterials are still being used in order to become products substitution for pre-implant surgery even though autologous bone grafts and allografts have been recognized for many years in surgical modality [7]. Besides drugs and artificial natural substances, a biomaterial is characterized as any blend of materials, where it can be used anytime for any tissue, organ or other function of the body substitution partially for sustaining the human's life expectancy [3,8]. Bone is a composed of organic and inorganic composites structure with a compound multiscale arrangement. Implant Biomimetic scaffolds for implantation of bone application ought to be planned with a basic and synthetic piece like local bone tissue. Under this point of view, scaffolds of polymer/ceramic composite present as enhancement for mechanical properties and activity of biological contrasted with a polymer/ceramic substance itself. Strikingly, calcium phosphate (CaP) ceramics production, for example, hydroxyapatite (HA) and tricalcium phosphate (TCP) have great osteoconductivity and osteoinductivity, and they have been ordinarily utilized in orthopedic application as filler materials for deformities of bone or as coatings on metal implants; while, natural and engineered polymers, for example, chitosan, collagen (Col), hyaluronic corrosive, and poly(lactic corrosive) (PLA) have great biocompatibility and high flexibility [9–11]. There are two elements that both of them have been utilized in bone tissue engineering which is collagen and hydroxyapatite inferable from their amazing osteoconductive property. The composite scaffold of these two natural materials has been ended up being more helpful than a monolithic one. The bendable collagen properties build the fracture strength and reduce the hydroxyapatite hardness. Furthermore, the hydroxyapatite expansion to the matrix of collagen enhances the mechanical stability of the scaffold in both dry and wet conditions and quickens osteogenesis [12]. These biomaterials are chosen dependent on the required properties for the ideal application, including explicit mechanical properties, porosity, degradation profiles, biocompatibility, and adherence and fuse into adjoining tissue [13]. The extracellular matrix ECM is responsible for directing basic native ECM cellular functions such as migration, proliferation, and differentiation, which are all vital for effective tissue formation. Presence of proteins on ceramics promotes bone cells adhesion that directly influences morphology of cells [14,15]. Biomaterials ought to almost certainly oppose chemical impacts and mechanical stresses while being consistently encompassed with the tissues and body fluids. The most widely recognized classes of biomaterials utilized are metals, ceramics and polymers as in **Table 1** [16].

2 Bioactive Ceramics

There are several components together with bio-ceramics that have a guarantee in bone tissue engineering (BTE) as strong materials, with complimentary bioactivity. They are ceramic composites, amorphous glasses and crystalline ceramics. Bio-ceramics

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Table 1 Classification of biomaterials

Biomaterial	*Advantage*	*Disadvantage*	*Application*	*Example*
Metals and alloys	Strong, tough, ductile	Dense, may corrode, difficult to make	Load-bearing bone implants, dental restoration, etc	Nanostructured titanium and Ti-6Al-4V alloys
Ceramics	Biomert, bioactive, bioresorbable, high resistance to wear, corrosion resistance	Brittle, low toughness, not resilient	Low weight bearing bone implants, dental restoration, tissue scaffolds, bone drug delivery, etc	Nanoclay, HA, TCP
Polymers	Flexible, low density, resilient, surface modifiable, chemical functional groups	Low stiffness, may degrade	Tissue scaffolds, drug delivery, breast implant, sutures, skin augmentation, blood vessels, heart valves, etc	Collagen and PLLA nanofibers
Composites	Strong, design flexibility, enhanced mechanical reliability than monolithic	Properties may vary with respect to fabrication methodology	Tissue scaffolds, drug delivery, dental restoration, spinal surgery, load bearing bone implants, etc	HA-collagen, HA-PLA

Note: Michael, F.M., Khalid, M., Walvekar, R., *et al.*, 2016. Effect of nanofillers on the physico-mechanical properties of load bearing bone implants. Materials Science and Engineering: C 67, 792–806.

have been shown to have osteoconductivity, high compressive strength and good bone integration [17,18]. Calcium Phosphates (CaPs) are the most often composites that using crystalline bio-ceramics in BTE, somewhat because of their commonness in local tissue of bone. Several composites have been adjusted in BTE scaffolds that are Hydroxyapatite (HA), tricalcium phosphate (TCP) and biphasic calcium phosphate (BCP), where BCP is a composition of two materials [18].

2.1 Tricalcium Phosphate (TCP)

Among accessible scaffold materials, calcium phosphate-based ceramics speak to an interesting road dependent on tunable likenesses in both crystalline structure and chemistry between calcium phosphate ceramics production and bone apatite. Formulations of calcium phosphate-based have exhibited superb osteoconductivity and biocompatibility in reproductive surgeries for over 30 years. Tricalcium phosphate (TCP), as a standout amongst the most broadly utilized calcium phosphates in bone tissue engineering, has shown osteogenic properties, phase stability and solid bond arrangement with the host bone tissue in various research [19–21]. 3D-printed TCP-based scaffolds can be evaluated as an appropriate decision for the applications of bone tissue engineering [21]. One successful strategy for upgrading the bioactivity of 3D printed-scaffolds is to utilize a mix with a bioceramic, for example, β-tricalcium phosphate (β-TCP). β-TCP is a generally utilized ceramic biomaterial that has great bioactivity, osteoconductivity, biocompatibility and degradability [22]. The β-TCP bioceramic likewise emulates the chemical composition of local bone mineral and gives a decent situation to osteogenesis, osseointegration and guided recovery of bone tissue. The combination of polymer (PCL) and bioceramic (TCP) using 3D printer shown in **Fig. 1** below [23]. The surface morphologies of the scaffolds showed that the exterior of the scaffolds containing β-TCP were rougher and more permeable than the PCL control. Park *et al.* had foreseen where the consolidation of β-TCP into the scaffolds could give the improved bioactivity, Nano-sized surface highlights, and hydrophilicity. Thus, these composite scaffolds were required to possibly enhance absorption of water and in this way improve cell development and overall cellular behavior. The influencer of cell production, relocation and integration are the expanded stiffness, roughness and porosity of β-TCP-content scaffolds that seems high.

2.2 Hydroxyapatite

In 1980, Bonfield *et al.* was first presented Hydroxyapatite (Ca10 (PO4)6(OH) 2), HA as reinforcement in polymer composites. Hydroxyapatite-strengthened polymer composites recommend fascinating properties for the applications of biomedical as a result of the existence of HA enhances the material's biological properties. On the other hand, the polymer gives upgraded mechanical properties that permit the bone tissue engineering for their application [24]. HA is the significant constituent of the inorganic parts in natural bone. Since of amazing biocompatibility, bioactivity and osteoconductivity, it has pulled in impressive intrigued and been researched broadly in biomedical applications [25,26]. Hu *et al.* researches indicated that nHAP advanced the attachment and growth of steoblasts cultivated in vitro nHAP was in situ blended within the hybrid scaffolds and the mechanical properties were progressed successfully, which is for the most part owing to the arrangement of nHAP and the relations with natural polysaccharides. The in sito shaped nHAP able the hybrid scaffolds with great bioactivity by means of in vitro mineralization [26]. The key focal points of synthetic HAp are its bio- compatibility, deliberate biodegradability in physiological circumstances with great osteoconductive and osteoinductive capabilities. Synthetic Hap has moreover been broadly utilized to mend hard tissues such as bone, bone augmentation, coating of inserts or fillers for bone and teeth augmentation [27].

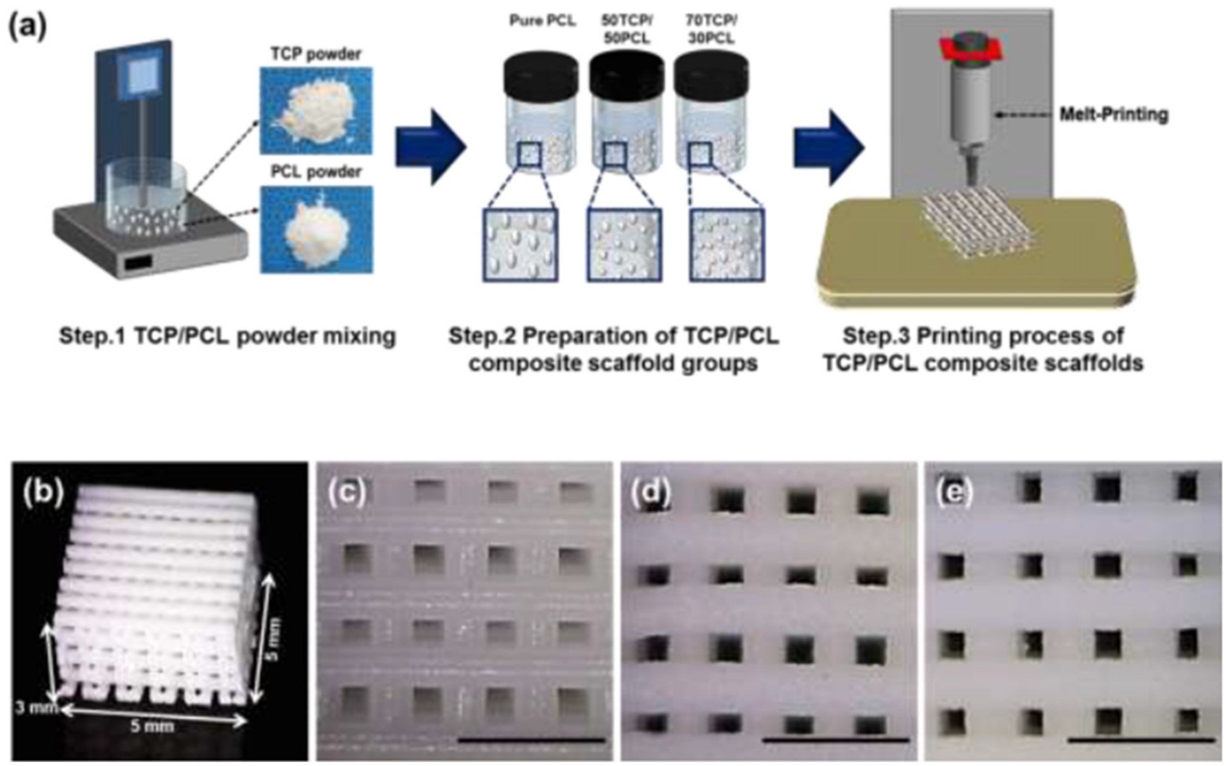

Fig. 1 (a) Schematic diagram of TCP/PCL composite scaffolds preparation and fabrication with the aid of 3D printing system using several samples of TCP and PCL, pictures of the scaffolds for (b) 3D, (c) PCL, (d) 50TCP50PCL, and (e) 70TCP30PCL, 2.5 mm of scale bar. Reproduced from Park, J., Lee, S.J., Jo, H.H., *et al.*, 2017. Fabrication and characterization of 3D-printed bone-like β-tricalcium phosphate/polycaprolactone scaffolds for dental tissue engineering. Journal of Industrial and Engineering Chemistry 46, 175–181.

2.3 Bio Glass

Composition of bioactive glass (BG) is comparable to the biological hydroxyapatite (HA) that has the particles composition of calcium and phosphate. The capacity of the particles makes them great composites to be attached to hard tissues in order to be utilized as biomaterials. The preferences of BGs over other bioceramics such as HA, tricalcium phosphate and etc., are their capacity to bond quicker to the bone, osteogenic properties and degradation within the body [28]. Especially, BG has special favorable superiority than different fillers in hard tissue engineering. BGs contain components, for example, silica (Si), calcium (Ca), phosphorus (P), and sodium (Na), which are available naturally in the body [29]. The radiant properties of osteoconductive and osteoinductive that contained in the bioactive glasses can connect to soft and hard tissues and emphatically influence the cell migration and separation. Most vitally, the discharged particles from bioactive glass would invigorate the genes appearance of osteoblastic cells and assist development the separation of osteoblastic and mesenchymal stem cells. Lian *et al*. compared the pure poly (octanediol citrate) POC elastomer, the POC/bioglass nanofiber composites shown quickened stimulation to the mouse bone marrow mesenchymal stem cells (MSCs) on the cell development and osteogenic differentiation [30,31].

3 Biodegradable Polymers

There are other important materials for platforms fabricate in tissue planning applications called polymers. In addition, variety kinds of biodegradable polymeric materials were used in this field, for example, naturally occurring materials, including polysaccharides [starch, alginate, chitin/chitosan, and hyaluronic corrosive (HA)] and proteins (soy protein, gelatin, collagen, fibrin gels, silk); (manufactured or designed polymers, for instance, poly(lactic corrosive) (PLA)), poly(glycolic corrosive) (PGA), poly (*ε*-caprolactone) (PCL), poly(hydroxyl butyrate) (PHB). The PLA, PGA, and their copolymers consist at least two monomers like poly (lactic-*co*-glycolic corrosive) (PLGA) that include in type of linear aliphatic polyesters, which are most often utilized in tissue engineering [32]. Synthetic biodegradable polyesters are the most preferred materials for applications of drug delivery and tissue engineering [33].

Table 2 Degradation profiles of PLA based formulations

Composition	*Degradation conditions*	*Degradation time*
PLA micro particles	In vitro: 0.1 M phosphate buffer, pH 7.4, 37 C	10%–30% weight loss after 40 days
PLA microspheres	In vitro: injection to rats livers	Implant conserved its geometrical from 14 months after injection
PLA fibers	In vitro: rat oral tissue	Full degradation between 42 and 70 days
PLA films	In vitro: 0.2 M citrate buffer, pH 7, 37 C	10% weight loss over 16 weeks
PLA implant	In vitro: transplantations to rats	14% weight loss after 3 months
PLA sheet	In vitro: transplantation in the infraorbital rim of macace monkeys	Remnants found at the surgical site 38 weeks post implantation
PLA plates	In vitro: subperiosteally in rabbits	70% loss of molecular weight after 42 days

3.1 Polylactic Acid (PLA)

In 1845, the French chemist known as Theophile-Jules Pelouze was being the first one who introduced Polylactic acid (PLA), via the poly-condensation of LA into low sub-atomic weight PLA, extending from 800 to 5000 g/mol. Afterward, Wallace Hume Carothers, who is the DuPont's chemist and also a designer of nylon, enhanced the generation procedure, empowering to build the normal atomic weight of the polymer to 100,000 g/mol. This enhanced the mechanical properties of PLA, besides ensure new possibility to contend with other commercial polymers. Nowadays, PLA is actually become the number two in worldwide ranking of most traded polymer [34]. PLA based formulations degradation profiles shown in **Table 2**.

PLA is the most important part of investigated polymers for good practices in bone tissue engineering [35]. The wide favor for PLA depends on its bioresorbability, biodegradability, biocompatibility, and flexibility. Santoro *et al*. have concluded that scaffolds of PLA Nano fibrous have appeared themselves to be a flexible instrument for tissue engineering, as a 3-dimensional topographical surface for cell development, a warehouse for drug delivery, and a substrate for bio-functionalization [35–37]. (PLA) could be a well-known synthetic polymer, broadly utilized to manufacture 3D scaffolds for tissue recovery due to its resorption nature; mechanical property and FDA endorsement for the clinical utilize [38].

3.2 Polycaprolactone (PCL)

Polycaprolactone (PCL) is a standout amongst the most widely recognized synthetic polymers in bone tissue engineering with appropriate properties, for example, biocompatibility, biodegradability, and higher toughness [39]. PCL is interesting because of its great biocompatibility, mechanical strength and processability, in any case, its high hydrophobicity and low degradability in vivo make it less reasonable for extensive haul purpose [1]. Among the polymers emerges PCL, for its better inflammatory reaction, slower resorption rate (required to keep up structural properties when utilized as bone fixation plates) and because of its hydrophobic character [40]. PCL is a semi-crystalline synthetic polymer that has a temperature of glass transition of −62°C and genuinely low melting point (55–60°C), which depends upon the degree of crystallinity. Fadaie *et al*. obtained bionanocomposite fibrous scaffold comprises of PCL and Nano fibrillated chitosan and appeared upgrade in mechanical properties, wettability and cellular compatibility of electro spun PCL-based scaffolds [41,42].

3.3 Poly Lactide-*co*-glycolide (PLGA)

Poly (lactide-*co*-glycolide) (PLGA) is a biocompatible and biodegradable polymer that has been broadly utilized in gadgets for tissue engineering and drug delivery usage [43]. Among all biomaterials, poly lactic-*co*-glycolic acid (PLGA) created as the foremost empowering substance that has potential to be utilized as carrier in drug delivery and can be scaffolds in tissue engineering. PLGA is a synthetic copolymer made out of glycolic acid and lactic acid monomers. Lactic acid is a 2-hydroxypropanoic acid or methyl-substituted glycolic acid that can be made in two shapes for example D and L by corn fermentation and other distinctive sources of agricultural [44]. Function of PLGA's properties in development of drug delivery showed in **Fig. 2**.

Physico-chemical properties of PLGA, for example, sub-atomic interaction potential, or biodegradation kinetics and swelling with implanted drugs, offer a few conceivable outcomes for the structure of controlled release systems. According to Takeuchi *et al.* when iontophoresis was applied on estradiol (E2)-loaded PLGA, they showed higher skin permeability than conventional nanoparticles both ex vivo and in vivo and improved bone mineral density of cancellous bone in an animal model for osteoporosis [45,46]. Specifically, the biodegradation rate of PLGA can be controlled by adjusting the proportion of lactide to glycolide and atomic weight of the copolymer. This is an imperative trademark because of that the biodegradation rate of composite should coordinate the speed of bone reproduction [47].

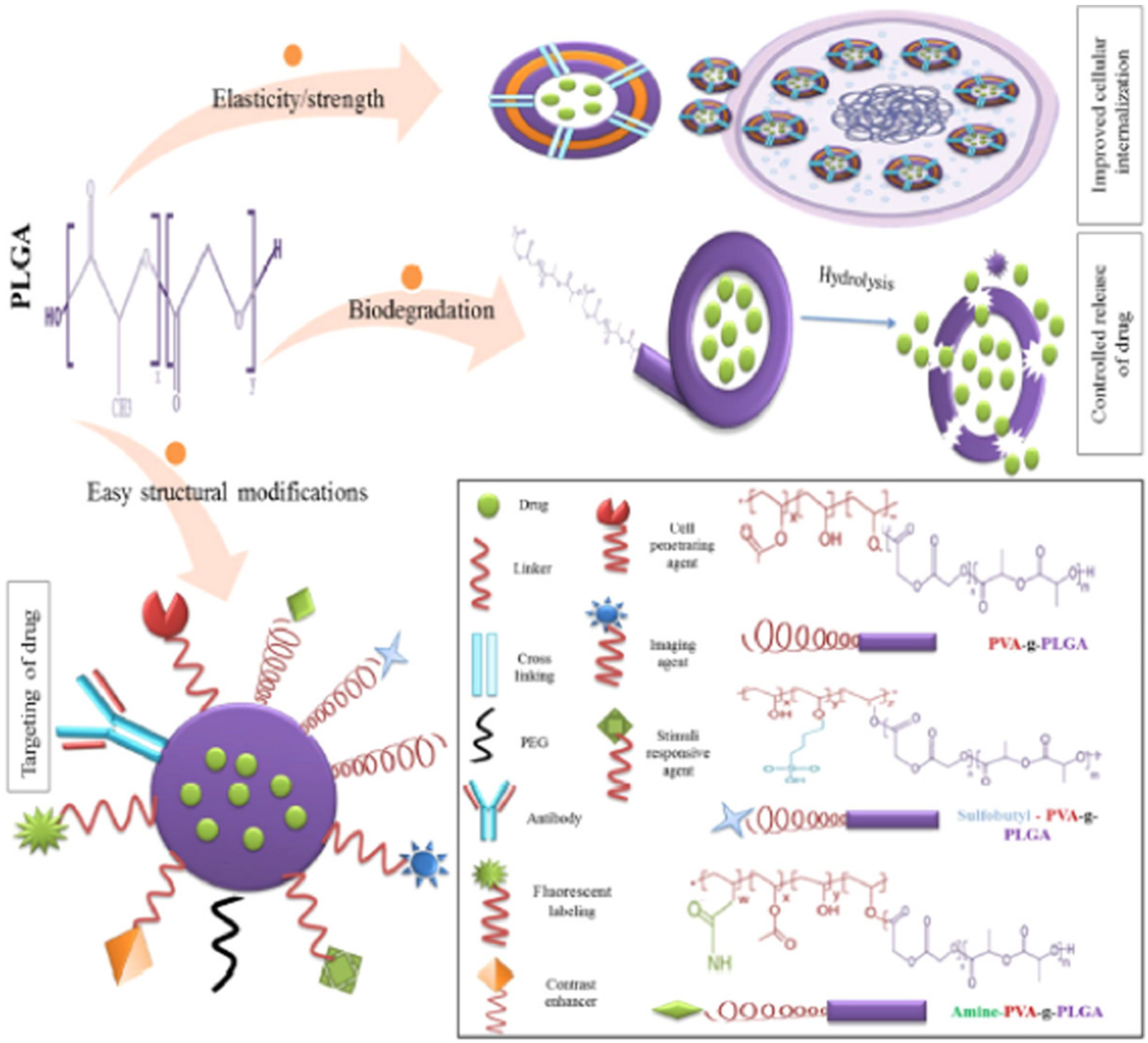

Fig. 2 Function of PLGA properties in development of drug delivery. Reproduced from Mir, M., Ahmed, N., ur Rehman, A., 2017. Recent applications of PLGA based nanostructures in drug delivery. Colloids and Surfaces B: Biointerfaces 159, 217–231.

3.4 Collagen

Collagen represents about 33% of all vertebrate body proteins. Collagen atoms are biodegradable, weakly antigenic, biocompatible, and have special self-assembling fibril-forming properties [48]. Collagen has been applied as a substance in artificial bone enthusiastically and mostly, it is found in bone (Type I) cartilage (Type II) and blood vessel (Type III) parts. As a natural polymer, it has astounding biocompatibility to let the development of cell and biodegradability so that the body can ingest successfully. The composition of Collagen-Hydroxyapatite (COL-HA) and microfibrillated cellulose (MFC) have been created become a composite by He *et al*. This type of composite was formed to be the material substitution of a new bone and the scaffolds are great with high level of cell development in biocompatibility in rate (>70%) and appropriate rate of hemolysis (≤5%) [49]. Common elements in the matrix of bone comprising of proteins, for case collagen that are surrounded interior of the calcified matrix. Until now, there are more than 28 sorts of collagen inside the vertebrates meanwhile four sorts of the collagen are being affirmed in the bone together with collagen type I, III, V and XXIV. In between all of the collagen types, collagen of type I is the most collagen that rich with protein up to 97% [50].

4 Conclusion

As of late, investigate exertion is being put within the progression of state-of-the-art tissue engineering strategies and biomedical implants facilitated to the upgrade or indeed restoration of the capacity of unfortunate tissues or organs. The engineering of biomaterials that not just fulfill all the desired prerequisites of the past however that can moreover balance the resistant framework, both inborn and versatile responses, is right now a critical objective of many studies. In this context, biomaterials are considered as key modulators of the immune reaction and hence can have critical impacts in tissue recovery and repair. It can be concluded that, over the past decades the usage of biomaterials for bone replacement have been improved and research is still going on to achieve the ideal goal.

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