01 Nov 2019

A Review of Materials for Managing Bone Loss in Revision Total Knee Arthroplasty

Romina Shafaghi

Omar Rodriguez

Emil H. Schemitsch

Paul Zalzal

et. al. For a complete list of authors, see https://scholarsmine.mst.edu/che_bioeng_facwork/1078

Recommended Citation

R. Shafaghi et al., "A Review of Materials for Managing Bone Loss in Revision Total Knee Arthroplasty," *Materials Science and Engineering C*, vol. 104, article no. 109941, Elsevier, Nov 2019.
The definitive version is available at https://doi.org/10.1016/j.msec.2019.109941

Materials Science & Engineering C 104 (2019) 109941

Contents lists available at ScienceDirect

Materials Science & Engineering C

journal homepage: www.elsevier.com/locate/msec

Review

A review of materials for managing bone loss in revision total knee arthroplasty

Romina Shafaghi[a,b], Omar Rodriguez[b,c], Emil H. Schemitsch[b,d], Paul Zalzal[e,f], Stephen D. Waldman[b,g], Marcello Papini[a,c], Mark R. Towler[a,b,c,*]

[a] Department of Biomedical Engineering, Ryerson University, Toronto M5B 2K3, Ontario, Canada
[b] Li Ka Shing Knowledge Institute, St Michael Hospital, Toronto M5B 1W8, Ontario, Canada
[c] Department of Mechanical Engineering, Ryerson University, Toronto M5B 2K3, Ontario, Canada
[d] Department of Surgery, University of Western Ontario, London N68 4V2, Ontario, Canada
[e] Oakville Trafalgar Memorial Hospital, Oakville L6J 3L7, Ontario, Canada
[f] Faculty of Health Sciences, Department of Surgery, McMaster University, Hamilton L8S 4L8, Ontario, Canada
[g] Department of Chemical Engineering, Ryerson University, Toronto M5B 2K3, Ontario, Canada

ARTICLE INFO

Keywords:
Bone loss
rTKAs
Augments
Bioactive glasses
Bone graft substitutes

ABSTRACT

In 2014–2015, 61,421 total knee arthroplasties (TKAs) were performed in Canada; an increase of about 20% over 2000–2001. Revision total knee arthroplasties (rTKAs) accounted for 6.8% of TKAs performed between 2014 and 2015, and this is estimated to grow another 12% by 2025. rTKAs are typically more complicated than primary TKAs due to the significant loss of femoral and tibial bone stock. The escalating demand and limitations associated with total knee arthroplasty and their revision drives the development of novel treatments. A variety of materials have been utilized to facilitate regeneration of healthy bone around the site of a knee arthroplasty. The selection of these materials is based on the bone defect size and includes bone grafts, graft substitutes and cements. However, all these materials have certain disadvantages such as blood loss, disease transmission (bone grafts), inflammatory response, insufficient mechanical properties (bone graft substitutes) thermal necrosis and stress shielding (bone cement). Recently, the use of metal augments for large bone defects has attracted attention, however they can undergo fretting, corrosion, and stress shielding. All things considered, this review indicates the necessity of developing augments that have structural integrities and biodegradation rates similar to that of human bone. Therefore, the future of bone loss management may lie in fabricating novel bioactive glass augments as they can promote bone healing and implant stability and can degrade with time.

1. Introduction

The number of revision total knee arthroplasties (rTKAs) is increasing due to the prevalence of primary total knee arthroplasties (TKAs) [1]. rTKAs are more complicated than TKAs since there is additional bone loss that influences implant stability [2–4]. The bone loss in rTKA occurs because of osteolysis, periprosthetic fracture or damage during primary implant removal [5].

There are a variety of materials that can be used to manage bone loss and improve implant stability. These include bone grafts, cements and metal augments. However, despite the introduction of these materials, management of large bone loss around the knee still represents a challenge. Several review papers identify the advantages/disadvantages associated with many of these materials [6–10]. However, each focuses on a certain class of materials, inhibiting holistic comparison. This paper serves as the first to review all available materials for addressing bone loss in rTKA, highlights their advantages and disadvantages and postulates future approaches to treating rTKA.

2. Bone loss (defect) in total knee arthroplasties

The common reasons for bone loss in rTKA include osteonecrosis (reducing blood flow which causes bone cell death), previous fracture of the tibial plateau or femoral condyles, cysts in bones, inflammation, bacterial infection, stress shielding, and osteolysis from wear and loosening of the implant resulting from the first surgery [11–13]. The

* Corresponding author at: Department of Biomedical Engineering, Ryerson University, Toronto M5B 2K3, Ontario, Canada.
E-mail address: mtowler@ryerson.ca (M.R. Towler).

https://doi.org/10.1016/j.msec.2019.109941
Received 19 January 2019; Received in revised form 14 June 2019; Accepted 2 July 2019
Available online 04 July 2019
0928-4931/

treatment of bone loss depends on its severity.

2.1. Bone loss classifications in rTKAs

The classification systems for bone loss in rTKAs include: 1) Dorr; 2) Rand; 3) Bargar and Gross; 4) Elia and Lotke; 5) Insall; 6) Slooff and de Waal Malefijt; 7) Anderson Orthopedic Research Institute; 8) Massachusetts General Hospital; 9) Clatworthy and Gross; 10) Huff and Sculco; 11) University of Pennsylvania and 12) Mount Sinai Hospital classification [14]. However, each of these has drawbacks, such as undefined defect size and morphology (Dorr classification), inaccurate preoperative assessment (Clatworthy and Gross classification) that can make them difficult to use [15] [16,17]. One of the best quantitative classification systems is that of the Anderson Orthopedic Research Institute (AORI) [13], this gives both defect size and location and suggests the most suitable treatment for each defect [18]. This classification is based on the condition of the metaphyseal part of bone (Fig. 1). There are three categories in this classification [19,20]:

Type 1: Intact metaphyseal bone, which does not have any effect on the stability of the components (minor bone defect).

Type 2: Damaged metaphyseal bone, in which the use of cement filling, augments or grafting is necessary (loss of cancellous bone).

Type 3: Deficient metaphyseal bone, in which the defects are associated with collateral or patellar ligament detachment and require the use of bone grafts or custom implants.

3. Current treatment options

There are different methods for dealing with bone loss including grafts, cementation with or without screws and metal augments [10]. Factors considered in bone loss management are the patient's age, life expectancy and bone quality (including microstructure, turnover and composition) [22].

3.1. Bone grafts

The use of grafting in joint arthroplasty is one of the most common treatments for bone loss [23]. Every year, > 2.2 M bone graft procedures are performed worldwide to manage bone loss in orthopedics, neurosurgery and dental implantation [23]. Grafts stimulate osteoconduction, and fill the void around implants [7,24].

The three main types of bone grafts are autografts, allografts and synthetic grafts [25]. Autografts are considered the gold standard since they have osteogenic, osteoconductive and osteoinductive characteristics [9]. A graft is usually harvested from the patient's iliac crest, distal femur, proximal tibia or medullary canal [26–29]. However, its use can lead to chronic pain, infection, wound complications, blood loss and other morbidity associated with surgical risks at the site of the tissue harvest [30]. Furthermore, there are some limits as to how much bone tissue can be harvested [9]. Allografts are made from bone harvested from donors or cadavers. The advantage of using allografts over autografts is the elimination of the possibility of donor site morbidity, but there are concerns including the risk of disease transmission from the donor to recipient, immune rejection, cost, delayed graft incorporation and reduced strength due to the use of gamma radiation for sterilizing the grafts [31]; it has been reported that doses over 30 kGy can retard graft strength through two mechanisms; directly, by breaking the polypeptide chain (in the dry state), and indirectly, through radiolysis of the molecules of water which can create free radicals that target the collagen [32]. Although bone grafts represent a $2.5B annual worldwide market [33], their limitations have necessitated the pursuit of natural (biologically organic compounds) or synthetic (organic/inorganic compounds) graft substitutes for the millions of bone graft operations that are carried out worldwide each year [34].

3.2. Bone graft substitutes

Laurencin *et al.* classified bone graft substitutes into five groups

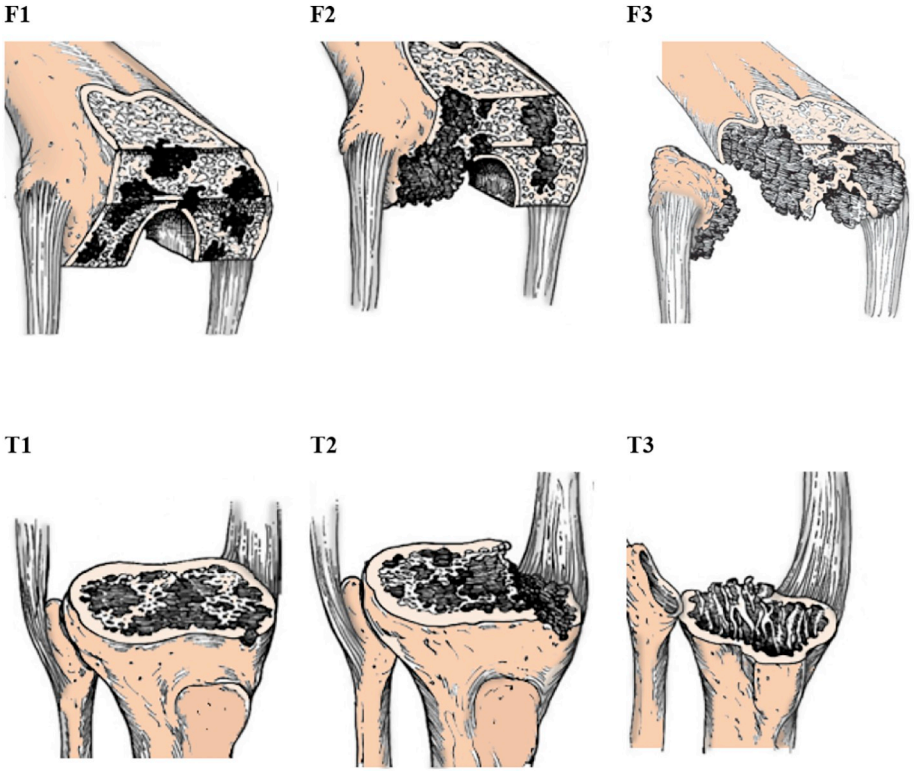

Fig. 1. F1, F2, and F3 are three types of femoral defect and T1, T2, and T3 are three types for tibial defect. F1 and T1 have an intact metaphyseal bone. F2 and T2 have a damaged metaphyseal bone. F3 and T3 have a deficient metaphyseal bone. Adapted from Pécora *et al.* [21].

Table 1
Modified classification of bone graft substitutes [9,35].

Category		Description	Examples
Natural	Allograft-based	Allograft bone used alone or in combination with other materials	Allogro® (AlloSource, Colorado, USA)
	Xenograft-based [34]	Used alone or in combination with other materials (bovine bone, porcine bone, and corals)	Hypro-Oss® (Bioimplon GmbH, Munich, Germany), Biocoral™ (Biocoral Inc., Delaware, USA)
	Factor-based	Natural and recombinant growth factors used alone or in combination with other materials	BMP-2 (Medtronic plc, Dublin, Republic of Ireland), BMP-7 (Stryker Biotech LLC, MA, USA)
Synthetic	Ceramic-based	Includes calcium sulfate, calcium phosphate, and bioactive glass alone or in combination	Novabone (Novabone, FL, USA)
	Polymer-based	Both degradable and nondegradable polymers used alone and in combination with other materials	Fisiograft®, (Ghimas s.r.l., Casalecchio di Reno BO, Italy)
	Composites	Combination of two or more different materials (*e.g.* polymer/ceramics) for the desired application	Cerosium™ (Haeger Potteries Inc., Illinois, USA

based on material sources and origin (natural or synthetic): allograft-based, cell-based, factor-based, polymer-based and ceramic-based [9]. This classification includes some materials in the developmental stage [24]. The modified Laurencin *et al.* classification is shown in Table 1.

3.2.1. Natural bone graft substitutes

3.2.1.1. Allograft-based graft substitutes. The use of allografts has increased since the 1980s. The increase in the number of joint replacements, the demand for grafting and the limited availability of autografts led to the opening of the first bone bank in New York in 1947 [36]. However, as stated (Section 3.1), the use of allografts has been associated with an increased risk of immunological response (donor-recipient antigen mismatches) [37,38]. Allografts can be customized and they are available in different forms, including cortical allografts, cancellous allografts, morselized allografts, structural allografts and demineralized bone matrix (DBM) [39]. Cortical allografts are used when load bearing resistance is required. They are free of bone marrow and blood. Cancellous allografts have poor mechanical properties; as a result, they are used as fillers. However during treatment, the osteoinductive potential of the grafts may be compromised due to missing viable cells, growth factors such as bone morphogenetic proteins (BMPs) [40] and collagen and non-collagenous proteins [41]. DBM is a highly processed allograft, which 60% of its mineral content has been removed during the demineralization process with acid [42]. Consequently, DBM has poor mechanical properties, and it is mainly used for filling bone defects when load bearing resistance is not required. However, the presence of BMPs, collagen and non-collagenous proteins provide DBM osteoinductive and osteoconductive potentials [43]. Recently, DBM has been incorporated into several products such as Allogro® (AlloSource, Colorado, USA), which is a combination of DBM with calcium sulfate. However, the risk of transmitting diseases and infections described in Table 3, and resorption of the graft still limit the use of allograft - based graft substitutes [44]. Some of the clinical findings of using allografts for revision total knee arthroplasty are collated in Table 2.

3.2.1.2. Xenograft-based graft substitutes. Xenografts are materials taken from a family, genus or species other than human [53]. The use of bovine bone was introduced in 1957 [54]. Diesel *et al.* used lyophilized bovine bone graft (Orthogen - Baumer) along with a tantalum wedge to reconstruct the acetabular in total hip arthroplasty in 15 patients. Authors reported comparable results to reconstructions performed using impacted grafts [55]. Charalambides *et al.* used Surgibone (Unilab, Inc., NJ, USA), a mixture of bovine bone apatite and protein with autograft to fill defects in the acetabulum and the proximal femur in revision surgery in 27 patients. The authors showed 25% of the patients needed re-revision because of graft rejection, MRSA deep infection and loosening [56]. Thus, the grafts derived from bovine bone still have the potential for transferring disease and causing a host immune response [57]. In the 1970s, another source of xenograft, derived from the exoskeleton of coral, was introduced [7]. Coral exoskeleton consists of 98–99% calcium carbonate in the form of aragonite (the high-pressure form of calcite), 0.5–1% of trace elements such as Sr, Mg, and F and ~0.07% of amino acids [58,59]. It has been reported that coral bone grafts are biocompatible, resorbable, osteoconductive and can be used clinically for spinal fusion, fracture repair, replacement of harvested iliac bone and craniofacial bone defects [7,60]. Corals are not osteoinductive or osteogenic, but by addition of growth factors or bone marrow cells, they can stimulate bone formation [60]. As shown in Table 4, coral's mechanical properties are influenced by their growth direction; corals that grow vertically (such as *Porites*) have better resistance to mechanical strains than those grown horizontally (such as *Acropora*) [61]. Biocoral™ (Biocoral Inc., Delaware, USA) is a commercially available coral-based graft, and use of this biomaterial can lead to complete bone regeneration within 6 months [59]. Nicolaides *et al.* used a coral wedge for treatment of valgus deformity of the knee with an open supracondylar osteotomy in 2 patients. The results showed partial absorption and complete incorporation of the wedge with the bone [62]. Although the results of using coral as bone graft substitutes in different parts of the human body are promising [63,64], no clinical studies related to the performance of this product in rTKA have been reported to date.

3.2.1.3. Factor-based bone graft substitutes. Studies have shown that materials such as bone morphogenetic proteins, BMP-7 (Stryker Biotech LLC, MA, USA), and BMP-2 (Medtronic plc, Dublin, Republic of Ireland), which are members of the growth factors-β (TGFβ)

Table 2
Clinical results of using allografts for the treatment of revision knee arthroplasty.

	Number of knees/grafts	United to the host bone	Dislocation & loosening	Fracture & nonunion	Infection
Massive allograft Mnaymneh *et al.* [45]	14 grafts	12	2	2	1
Clatworthy *et al.* [46]	52 knees	NA	5	2	4
Structural allografts Engh *et al.* [47]	46 knees	NA[a]	0	0	2
Steens *et al.* [48]	34 knees	NA	5	2	NA
Malhotra *et al.* [49]	1 knees	2	0	0	0
Lee *et al.* [50]	2 knees	4	0	0	0

[a] Not available.

Table 3
Risk of transmitting diseases and bacterial infections in allograft - based grafting (containing marrow).

	HIV	Hepatitis C	Bacterial infections	
Risk of transmitting diseases, and infections	0.03% [44]	0.01% [44]	Massive allografts[a] 12% [51]	Non-massive allografts 0.7% [52]

[a] Massive allografts are used for large bone defect treatments.

Table 4
Mechanical and physical properties of two coral genera compared to trabecular and cortical bone [61].

Mechanical & physical properties	Porites	Acropora	Trabecular bone	Cortical bone
Porosity %	47–51%	20–30%	50–90%	5–30%
Compressive strength (MPa)	20–31	78–142	1–12	150–200
Young's modulus (GPa)	7.62–8.36	21.3–27.9	0.050–0.4	17
Direction of growth	Vertical	Horizontal	Horizontal	Horizontal

Table 5
Clinical results of using BMPs for the treatment of long bone defects.

Authors	Follow-ups (months)	Number of patients	Healing rate %
Jones *et al.* [75]	12	15	86.7
Swiontkowski *et al.* [76]	24	66	90.9
Zimmermann *et al.* [77]	49	26	92
Giannoudis *et al.* [78]	Range 12–65	45	100
Desai *et al.* [79]	32	9	100
Convay *et al.* (BMP-7) [80]	8	76	70
Convay *et al.* (BMP-2) [80]	5	138	93

superfamily, induce bone formation in tibial non-unions at the same rate as autografts, and they can also accelerate tibial fracture healing (it is still a controversial subject [65]) [66,67]. BMP's effect on bone formation has been demonstrated through numerous animal trials [68]. Gessink *et al.* used BMP-7 to fill the bone defect in a human fibula for the first time [69]. The authors showed the efficacy of BMPs in critical bone defect healing in humans [69]. In 2001, Friedlaender *et al.* demonstrated that BMPs are clinically safe osteogenic materials for the treatment of tibial non unions and the results are comparable to those achieved using autografts [66]. In a 2004 two-year follow-up study, Jager *et al.* showed using BMP2 in revision total hip surgery (rTHA) promoted bone formation in critical sized bone defects [70]. The US Food and Drug Administration (FDA) approved the use of BMP-2 as a bone graft substitute for tibial fractures in 2004 [71]. These materials induce a sequential cascade of events for chondro-osteogenesis including chemotaxis, proliferation of MSCs and osteoprogenitor cells and differentiation into a chondrogenic or osteogenic lineage [72,73]. Furthermore, their use reduces operating time and surgical blood loss in comparison with autologous bone grafts [74]. Clinical studies using BMPs for the treatment of long bone defects are summarized in Table 5.

Although BMP use is becoming more common in the treatment of bone fractures, it has only been reported in one revision arthroplasty study [66,76,81] [70]. Using high dosages (mg level) of these materials in order to obtain the desired osteoinductive effect (natural endogenous production is at the ng level) [71] can lead to inflammation, induction of adipogenesis and osteoclast activation [82]. The reason for the adverse effects of BMPs is believed to be correlated with their pleiotropic (multiple phenotypic expression) effects, including activation of peroxisome proliferation-activated receptor gamma (PPARγ) signaling which leads to adipocyte (fat cell) formation [83], inflammatory cytokines and chemokines, and tumor necrosis factor (TNF)-α [84]. As a result, more studies are needed in order to reduce their side effects. The limitations of natural bone grafts have necessitated the pursuit of alternative synthetic bone grafts, including natural and synthetic polymers, ceramics, composites and metals [9].

3.2.2. Synthetic bone graft substitutes

3.2.2.1. The evolution of synthetic grafts. The evolution of synthetic grafts is divided into three generations [85]. The first generation included metals such as stainless steel and titanium, ceramics, and polymers including silicone and poly(methylmethacrylate) (PMMA) [86]. The problem with these materials is the formation of fibrous tissue (densely-packed collagen fibers with few cells) as a protective mechanism that eventually surrounds the grafts and leads to aseptic loosening [87]. In the second generation, in order to avoid fibrous tissue formation, bioactive and biodegradable materials were used. These materials are able to interact with the biological environment and exchange ions with body fluid. The materials are designed so that their rate of degradation matches the regeneration rate of new tissue [7]. The third generation of synthetic grafts attempted to make three-dimensional scaffolds that can serve as osteoconductive matrices, incorporating bone progenitor cells and growth factors, in order to enhance bone formation [7,88]. The goal of a synthetic graft is to bring together functional constructs that restore, maintain, or improve damaged tissues [89]. The success of bone graft materials depends on their biological activity and the incorporation of the constructs with surrounding tissues as well as their mechanical properties, for supporting loads and resisting stresses [90].

3.2.2.2. Ceramic-based bone graft substitutes. Ceramic-based bone graft substitutes have been used in dentistry and orthopedics since the 1970s and 1980s, respectively [91]. Bioceramics are classified into three groups according to the response of tissue to them: nearly bio-inert (*e.g.* alumina and zirconia), bioresorbable (*e.g.* tricalcium phosphate), and bioactive (*e.g.* bioactive glasses, bioactive glass-ceramics) [92].

Bioceramics can be single crystals (sapphire), polycrystalline (alumina or hydroxyapatite), amorphous (Bioglass®) or partly amorphous (glass/ceramics) [87]. Bioceramics vary in their biocompatibility, osteoconductivity, osteoinductivity and compressive strength according to their composition [93]. However, they have relatively low tensile and fracture strengths and poor resistance to shear stresses and fatigue [94,95].

3.2.2.2.1. Calcium sulfate. Calcium sulfate (Plaster of Paris) is a ceramic bone graft substitute that was first used in orthopedics in the 10th century [96]. Calcium sulfate has been used as a filler for bone loss since the late 1800s [97]. In 1892, its suspension in 5% phenol was used to treat tuberculous osteomyelitis [89]. Calcium sulfate is osteoconductive and biodegradable; in a multicenter trial, calcium sulfate was used alone and/or with other materials, such as bone marrow, demineralized bone matrix or autograft, for the treatment of patients with bone defects. The clinical results showed that 99% of the calcium sulfate had resorbed in all the patients, and 88% of the defect from each patient was filled [98]. Kallala *et al.* used Stimulan bio – absorbable calcium sulfate beads on 755 patients who underwent revision arthroplasty (456 rTKAs and 299 rTHAs) with a follow-up of

Table 6
Overview of the outcomes of calcium sulfate in contact with hard tissues.

Type of calcium sulfate	Resorption %	Bone formation %	Complication %
Osteoset pellets [98]	99	88	3.6
Calcium sulfate powder [105]	86.7	86.7	53.3
Plaster of Paris pellets [106]	NA[a]	NA	15.4

[a] Not available.

78 months. They indicated the safety and effectiveness of calcium sulfate as a bone graft substitute [99].

Walsh *et al.* hypothesized that calcium sulfate can promote bone remodeling due to the demineralization of adjacent bone caused by the reduction in pH of the local environment (bone resorption). This demineralization leads to the release of BMPs which are osteoinductive agents for bone healing (bone formation) [100]. Furthermore, it has been shown that the compressive strength of calcium sulfate in its set form (~23 MPa) is greater than cancellous bone [89]. In addition, calcium sulfate is cost effective (Osteoset resorbable mini bead kit is about $329.95) and available as pellets (Osteoset, Wright Medical, Amstelveen, The Netherlands) and an injectable iteration (MIIG, Wright Medical, Amsterdam, The Netherlands) [101]. Since calcium sulfate induces ingrowth of blood vessels, it must be used next to viable periosteum or endosteum [102]. However, calcium sulfate needs a dry environment within which to set. Furthermore, studies have shown that with calcium sulfate grafts, the rate of resorption (4 to 12 weeks) is more rapid than bone formation (6 to 12 weeks) [101,103], leading to debate about whether calcium sulfate can provide long-term three dimensional structural support [104]. Some of the clinical outcomes of using calcium sulfate as bone graft substitutes are shown in Table 6.

3.2.2.2.2. Calcium phosphate. The first successful application of calcium phosphate ceramic for bone defect repair in humans was in 1920 [107], and in 1971, it was indicated for dental applications [108]. Calcium phosphates are available in a variety of compositions, including hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$), tricalcium phosphate (TCP, $Ca_3(PO_4)_2$) and biphasic calcium phosphates (BCP, consisting of an intimate mixture of HA and β-TCP of varying HA/β-TCP ratios). Calcium phosphates have been employed in the repair of skeletal defects because they are biocompatible [109], osteoconductive [110] and biodegradable [111]. Furthermore, calcium phosphates can serve as carriers of BMPs, bioactive peptides, or MSCs [112] that induce bone regeneration. However, different calcium phosphates have different strengths and degradation rates. For instance, the fracture toughness and tensile strength of HA and β - TCP are 0.4–0.7 $MPa.m^{1/2}$, 1.3 $MPa.m^{1/2}$ and 18 MPa, 12.5–20 MPa, respectively; lower than natural bone (2–12 $MPa.m^{1/2}$ and 7–30 MPa) [113,114] [33,115–117]. As a result, in order to use calcium phosphates in large bone defects and in load bearing applications, their mechanical properties, including fracture toughness and tensile strength require improvement [118]. Some of the clinical outcomes of using calcium phosphates as bone graft substitutes are shown in Table 7.

3.2.2.2.3. Bioactive glasses. These are a group of materials composed of acidic oxides (*e.g.* phosphorus pentoxide, silicon dioxide, borate oxide and aluminum oxide) and basic oxides (*e.g.* calcium oxide, magnesium oxide, zinc oxide). This group is termed bioactive because the materials can develop an active HA layer (similar to the mineral phase of bone) on their surface which can bond with bone and soft tissues [123]. The first bioactive glass was invented by Hench *et al.* in 1969 [124,125]. This silicate glass has a composition of 46.1 mol% SiO_2, 24.4 mol% Na_2O, 26.9 mol% CaO and 2.6 mol% P_2O_5, and was later named 45S5 Bioglass® [126]. Bioactive glasses initiate biological responses by releasing ions into the surrounding area [127]. One feature of bioactive glasses is their compositional flexibility and, as a result, there are several types of bioactive glass [128]. This review will focus on three bioactive glass types: silicate-, phosphate- and borate-based glass,

3.2.2.2.4. Phosphate bioactive glass. Phosphate glasses have been studied for 150 years [129]. However, their applications have been limited, until it was determined that the addition of 30 mol% of metal oxides such as TiO_2, CuO, NiO, MnO, and Fe_2O_3 reduced their solubility [130]. Metal oxides can increase cross-linking within the glass structure, decreasing dissolution rate [131]. Consequently, metals that have antibacterial properties can be incorporated into the glass and released as the glass dissolves [132]. Phosphate bioactive glasses are based on phosphorus pentoxide (P_2O_5), a glass network former, and calcium oxide (CaO) and sodium oxide (Na_2O), network modifiers [133,134]. The affinity of P-O-P bonds towards hydration, and the asymmetric nature of the phosphate PO_4 tetrahedron reduce phosphate glass durability [135,136] [132]. Phosphate-based bioactive glasses can be used in both soft and hard tissue engineering. In bone, phosphate glasses are used in combination with polymers. Vitale-Brovarone *et al.* prepared GC-ICEL2 (phosphate-based glass of the composition 3 mol% SiO_2, 25 mol% Na_2O, 26 mol% CaO, 45 mol% P_2O_5, 7 mol% MgO, and 4 mol% K_2O) scaffold from the combination of bioresorbable phosphate glass (I-CEL2), and polyethylene particles to obtain a scaffold with interconnected pores and high porosity [137]. Trabecular scaffolds made from phosphate glass using hydrogen peroxide (H_2O_2) for foaming have also been fabricated [138]. Changing thermal conditions and H_2O_2 concentrations in these scaffolds can affect both pore sizes and porosity [138].

3.2.2.2.5. Silicate bioactive glass. Bioactive glasses are traditionally based on a silicate backbone [139]. The key features that are responsible for the bioactivity of silicate bioactive glasses are the

Table 7
Clinical applications and effects of different types of calcium phosphates in contact with hard tissues.

Names	Years	Effects	Applications
Interporous HA [119]	1989	Safe, and osteoconductive, but demonstrated slow biodegradation	Tibial plateau fractures
HA coatings [120]	2001	Promoting faster and stronger fixation and stimulating bone growth	Femoral stems, dental and knee implants
Tricalcium phosphate [121]	1989	Promoting osteoconducting ability, reduced operating time	Fractures in different parts of the human skeletal system (femur, tibia, humerus, *etc.*,)
BCP (Triosite™[a] and Bicera™[b]) [122]	2017	Stimulating bone formation	Rabbit femoral condyle defects

[a] Zimmer, USA.
[b] Wiltrom Ltd., Taiwan.

Table 8
Compositions of 45S5, 13–93, 6P53P (BonAlive®) glasses, 45S5.4F, 52S4.6, and 42SF [144].

Composition (wt%)	45S5	13–93	6P53B	45S5.4F	52S4.6	42SF
Na_2O	24.5	6.0	10.3	24.4	21.5	26.3
K_2O	0	12.0	2.8	0	0	0
MgO	0	5.0	10.2	0	0	0
CaO	24.5	20.0	18.0	10.8	23.8	17.4
SiO_2	45.0	53	52.7	46.1	52.1	42.1
P_2O_5	6.0	4.0	6.0	2.6	2.6	2.6
CaF_2	0	0	0	10.8	0	11.60

lower percentage of SiO_2 (< 60 mol%) [140], the higher percentage of Na_2O and CaO (glass network modifiers) and the higher CaO/P_2O_5 ratio compared to normal silicate glasses [141]. Different series of silicate–based bioactive glasses with different compositions have been synthesized by using traditional melting methods and sol gel techniques [142,143]. As shown in Table 8, the base components of most silicate bioactive glasses are similar to those in 45S5 (Bioglass®), but some of them, such as 13–93 glass, have additional modifiers, K_2O and MgO [144].

Silicate bioactive glasses are osteoconductive, and they facilitate HA formation and bond directly to pre-existing bone and soft tissues [118,145,146]. Despite the extensive studies using silicate bioactive glasses, their osteoinductive potential still under debate [147] [87,148]. However, their low compressive strength and high Young's modulus restrict their applicability for load bearing (Table 9) [149,150].

Different methods have been evaluated to improve the mechanical properties of silicate-based bioactive glass scaffolds. Wu *et al.* used rice husks for foaming 45S5 Bioglass and sintered the resultant material at 1050 °C. They achieved promising results from mechanical and degradability tests in simulated body fluid (SBF) [152]. Compressive strengths were in the range of those of trabecular bone [152]. In other studies, sucrose was used as a macropore former to fabricate nano-macroporous soda lime phosphosilicate glass scaffolds and the results indicated an improvement in bone regeneration [153]. Other studies indicated that nano-sized bioactive glass (nBG) in a dense collagen-nBG hybrid gel (DC-nBG) increased the osteoconductivity and the stiffness of the scaffolds when compared to micro-sized bioactive glass (μBG) scaffolds, by increasing the surface area to volume ratio and calcium phosphate formation rate [154,155].

Amorphous bioactive glasses can be crystalized at high temperature leading to changes in their strength, biodegradability and bioactivity [155]. At a higher temperature, the nucleation rate will be lower and crystal growth rate will be higher, resulting in the formation of a small number of larger crystals, and thus larger pore sizes [156]. As a result, Chang *et al.* used an advanced heat treatment to develop a novel bioactive glass BG20 (34 wt% SiO_2, 5 wt% MgO, 45 wt% CaO, 16 wt% P_2O_5) with different crystal structures. By altering the temperature (800–950 °C) [157], they showed that BG20 had the potential to develop endochondral ossification in addition to the capacity for osteogenesis. However, additional tests are still needed to explain the regulation mechanism of BG20 on the differentiation of bone marrow stromal cells (BMSCs) [157].

Beall *et al.* showed chain silicates based on potassium fluororichterite ($KNaCaMg_5Si_8O_{22}F_2$) compositions have bone forming potential along with flexural strengths (> 200 MPa) and fracture toughnesses (> 3 MPa $m^{1/2}$) which are 5 and 27 times, respectively, higher than those of 45S5 bioactive glass [158–160]. Bhakta *et al.* modified potassium fluororichterite compositions by substituting CaO for MgO and adding P_2O_5. The new compositions were not only osteoconductive, but also had higher fracture toughness and biaxial flexural strength [161,162]. However, their potential for bioactivity is still under investigation [161]. Some of the clinical outcomes after using silicate bioactive glasses have been shown in Table 10.

3.2.2.2.6. Borate bioactive glass. Due to the limitations of silicate-based bioactive glasses such as their slow and incomplete conversion to HA in body fluid [166], Brink *et al.* proposed the use of boro-silicate glasses in which variable amounts of borate oxide were added to the silicate-backbone [166–168]. The studies demonstrated that the conversion rate of the boro-silicate glasses to HA increased markedly with the increase of borate oxide content [169].

Borate glasses have lower chemical durability than silicate glasses, therefore they can convert more completely and more quickly to an HA-like material [166,170]. The conversion process of borate glass to HA is similar to 45S5 glass, with the formation of borate–rich layers similar to SiO_2 rich layers [169,171]. Borate bioactive glasses induce cell proliferation, differentiation and tissue infiltration [169,172,173]. Fu *et al.* showed that borate bioactive glasses promote bone formation faster than 45S5, thus reducing rehabilitation time [174]. Huang *et al.* showed that the degradation rate of the silicate bioactive glasses can be controlled by replacing the SiO_2 partially or fully with B_2O_3 [166,175]. The simplicity of fabrication and control of degradation rate of borate-based glasses make them promising for bone formation. Furthermore, their compositional flexibility makes them a source of essential elements (*eg.* Zn, Cu, and Sr) for bone growth and bacterial inhibition [141]. The first borate glass scaffold was derived in 2005 [172,176] and the concentration of boron (< ~126 mg/kg/day) released from it into the bloodstream had no harmful effects on human health [141,169,177]. Some of the clinical findings of using borate bioactive glasses have been shown in Table 11.

3.2.2.3. Synthetic composite grafting. The purpose of using synthetic composite grafts is to unite the materials in more controlled and effective combinations than are found naturally in autografts [23]. Most composites [184] are composed of a hard dispersed phase, to prevent the movement of the matrix, and a matrix phase that functions as a stress transfer medium [185,186]. Composition of S53P4 + PMMA is a synthetic composite graft, using for human craniofacial bone reconstruction [187]. Cerosium™ (Haeger Potteries Inc., Illinois, USA), used in mandibular prostheses, is another example of a composite made of a polymer (low elastic modulus) matrix and a bioceramic (high biocompatibility) dispersed phase [188,189]. However, the bond between the polymer and polymer-ceramic bond degrades which can result in failure [190].

3.2.2.4. Polymer-based bone grafting. The use of biodegradable polymers in orthopedic surgery started in the 1980s [191]. Polymers

Table 9
Physical and mechanical properties of bone and silicate bioactive glasses [149–151].

Material	Density (gr/cm^3)	Porosity %	Compressive strength (MPa)	Young's modulus (GPa)
Cortical bone	1.6–2.1	5–10	130–180	7–30
Cancellous bone	1.0	50–90	4–12	0.05–0.5
45S5 Bioglass®	2.7	NA[a]	~500	35
Porous 45S5 Bioglass®	NA	89–92	0.27–0.42	NA
Porous bioactive glass 70S30S	~0.58	82	2.25	NA

[a] Not available.

Table 10
Overview of the clinical findings after using silicate bioactive glasses.

Type of glass	Year	Applications	Achievements
Solid, cast Bioglass® [163]	1986	Middle ear bone reconstruction	Bond firmly to soft and hard tissues
NovaBone [87]	1993	Maxillofacial reconstruction	Elimination of cost, time, pain compared to bone autografts
PerioGlas® (Henry Schein, NY, USA) [164]	1998	Jaw bone defects	Induction of bone formation, no harmful reactions
S53P4 BoneAlive® [165]	2000	Orbital floor fractures	Osteoinductive, low degradation rate with sufficient mechanical support
Cones of Bioglass® [125]	2006	Providing a stable ridge for denture construction after tooth extraction	Bond to bone

are divided into two groups; natural and synthetic [192]. The most common polymers used as bone graft substitutes are shown in Table 12.

Most of the biodegradable synthetic polymers used for fabricating scaffolds are saturated poly-α-hydroxy esters [199] [200]. These polymers, including poly–L-lactic acid, polyglycolic acid are degraded first through hydrolysis (de-esterification) and then the monomeric components are removed through enzymatic and cellular pathways [200]. Therefore, the degradation of polymers can be modified through copolymerization and changes in hydrophobicity and crystalline structure [201]. Unfortunately, the crystals that develop from degradable polymers can lead to inflammation and osteolysis [192]. However, the possible risks of toxicity, immunogenicity and infections are lower for pure synthetic polymers with monomeric units [200]. Furthermore, the elastic moduli of some polymers such as polyurethanes are lower than natural bone; therefore, they are too flexible for load bearing solutions [202].

3.3. Bone cements

In the 1970's, the FDA approved the application of bone cements for hip and knee prosthetic fixation [203]. The term bone cement is commonly used for PMMA. However, there are other commercial bone cements such as calcium phosphate cements (CPCs) and glass polyalkenoate (ionomer) cements (GPCs), which are used in a variety of orthopedic and dental applications [203]. PMMA can be used for tibial defects of < 5 mm [15] alone (the full cementation technique) or combined with the other materials (the hybrid fixation technique). Full cementation has advantages over bone grafting, including quick fixation and adaptability to bone defect geometry [35]. Furthermore, PMMA has the potential for drug delivery [204]. However, it has some disadvantages including the risk of thermal necrosis due to its exothermic polymerization which causes denaturation of collagen [205], the potential for fat embolism during the pressurization of the cement in the femoral canal (injectable cement) [206,207], and the reduction of stress on the cancellous bone under the tibial base plate of a TKA which can cause bone resorption and eventual loosening of the tibial component [208]. Furthermore, in the case of further revision, the cemented component can be difficult to remove without fracturing the bone or bone loss [209,210].

The use of bone cement with screws was first introduced in 1982. Cement with screws can be used for small bone defects (AORI type-1, 5–10 mm). The screws can be titanium or 316 L stainless steel [211,212]. Cements with screw fixation exhibit less displacement of the prosthesis than cement alone, and the rate of rTKA failure with screws is less than without screws [213]. Moreover, the use of PMMA with screws can decrease the duration of the surgery by reducing the number of necessary cuts to the tibial plateau and femoral condyle [15,214]. However, there is still the risk of thermal necrosis and the appearance of radiolucent lines [15]. Also, screw augmented cementation cannot be used for poor quality cancellous bone [215], although it is more cost effective ($100–137 per screw) than augmenting with metal wedges ($910 – $2240 per wedge) [214]. Some of the clinical findings of cement for rTKAs were shown in Table 13.

3.4. Metallic scaffolds

Greenfield received the first patent for a metallic framework-based artificial tooth root in 1909 [217]. Greenfield used a hollow basket made of iridoplatinum wire soldered with 24 karat gold for implantation [218]. The metallic basket did not remain in implant dentistry because of bone resorption caused by excessive stress and lack of biocompatibility [218]. In 1974, Rostoker *et al.*, fabricated interconnected pore fiber metals for coating hip and knee replacement prosthetics. The coating can provide a porous surface for cell invasion and load distribution [219]. However, there are some problems with the use of porous metal coatings, including corrosion, and some difficulties in removing the replacement prosthetics in the case of revision or re-revision arthroplasties. Compared to other grafts, metallic materials offer a wider range of mechanical properties such as hardness, ductility, fracture toughness, and formability [220].

The most common metallic materials in orthopedic applications were stainless steel and cobalt-chrome-based alloys [86]. Stainless steel is biocompatible, resistant to corrosion, and cost effective. Orthopedic surgical stainless steel is 316 L (16–18 wt% Cr, 10–14 wt% Ni, 2–3 wt% Mo, 0.03% C, 2 wt% Mn, 0.75 wt% Si, 0.045 wt% P, 0.03 wt% S, and 0.1 wt% N) [221]. However, its use in orthopedics is not ideal because it has a low resistance to wear and a high Young's modulus of 193 GPa, which induces stress shielding [222].

In 1966, Co–Cr–Mo alloys were introduced in prosthetics [223] because of their high corrosion and wear resistance [224]. However, similar to stainless steel, they can result in stress shielding because of their high Young's modulus (230 GPa) compared to bone (3–21 GPa).

Table 11
Summary of the clinical findings after using borate bioactive glasses.

Type of glasses	Year	Applications	Achievements
45S5. 2B glass particles [178]	2005	Implantation in the contralateral tibia of rats	Showed an increase in bone formation and glass dissolution rate compared to 45S5 glass
Vancomycin-loaded borate glass pellets [179]	2010	Tibia of rabbits	No inflammatory response, induction of bone formation and blood vessel growth, good drug delivery
13-93B3 fibrous scaffolds [180]	2013	Rat calvarial defects	Stimulation of bone formation and glass degradation rate
Copper-doped borate glass fibers [181]	2013	Rat calvarial defects	Stimulation of osteoinduction and osteoconduction
Borosilicate glass scaffolds loaded with Fe_3O_4 magnetic nanoparticles [182]	2015	Rat calvarial defects	Increasing bone regeneration rate
Lanthanum-doped borate glass particles [183]	2017	Rabbit bilateral femoral defects	Enhancing bone formation

Table 12
Types of polymer-based graft substitutes.

Category		Applications	Results
Natural polymers	Collagen membrane [193]	Treating periodontal intrabony defects	No adverse tissue reaction, promotion of bone formation
	Chitosan gel [194]	Periodontal intraosseous defects	Stimulation of bone formation
	Silk-based devices [195]	Fracture fixation of rat Limbs	Biocompatible, low degradation rate, good mechanical properties, less inflammatory response
	Alginate membrane [196]	Wister rat bone defects	Biocompatible, Osteoinductive, degradable
	Hyaluronic acid [197]	Bone repair in human dental sockets	Biocompatible, non-immunogenic, osteoinductive
Synthetic polymers	Poly-L- lactic acid [198]	Dog distal femur defects	Biodegradable, immunogenic

Table 13
Overview of the clinical findings after using cement for rTKAs.

Bone cement	Number of knees	Infection	Aseptic loosening	Periprosthetic fracture	Failed at rate%	Follow-ups
Primary prosthesis and cement without screw [214]	182	NA[a]	NA	NA	3.3	15 years
Primary prosthesis and cement with screw [214]	179	NA	NA	NA	5.0	15 years
Full cementation [204]	18	1	0	0	5.6	4 years
Cementing technique [216]	206	6	0	1	3.4	2 years

[a] Not available

The lack of mechanical stimuli of adjacent bone can cause bone resorption and loosening of the implant [225]. Furthermore, the Ni, Cr and Co released from the stainless steel and Co–Cr–Mo alloys due to *in vivo* corrosion are potentially toxic [226].

Titanium (Ti) and its alloys exhibit reduced toxicity and a lower Young's modulus (110 GPa) compared to both stainless steel and Co–Cr–Mo alloys [227]. However, the processing of Ti and its alloys is difficult because of their high reactivity at high temperatures [228].

Magnesium alloys have also been used as substitutes [229,230] as they promote bone formation and are biodegradable [229]. Degrading porous magnesium alloy AZ91D (9 wt% Al, 1 wt% Zn, 0.15–0.5 wt% Mn, Mg balance) promotes osteoblast activity and reduces the number of osteoclasts [230]. The mechanical properties of commonly used metallic biomaterials are compared to cortical bone in Table 14.

Whilst the limited porosity of conventional porous metals such as titanium and cobalt-chrome sintered beads affect their potential for tissue ingrowth and implant stability, porous tantalum (porosity 75–80%, pore size 400–600 μm) are used for orthopedic surgery [232]. Clinical trials employing porous tantalum (Ta) indicate its biocompatibility and low Young's modulus (Table 14) [10,232,235]. Furthermore, Ta has biological advantages, including negative charge and interconnectivity of the pores, facilitating the formation of scaffolds with osteoconductive potential. However, its high cost is still a concern [236–239].

3.5. Megaprostheses (custom made prostheses)

The term megaprostheses was first introduced in an international work shop on the design and application of tumor prostheses in 1981 [240]. Megaprostheses offer suitable mechanical properties, immediate fixation and early weight bearing for managing complex bone loss in osteosarcoma around knee and rTKAs. However, manufacturing of megaprostheses is expensive and time consuming [241]. Furthermore, there are always risks of mechanical complications and infections. Thus, the overall survival rate of megaprostheses is low [242] [243]. Some of the clinical findings of using megaprostheses are shown in Table 15.

Table 14
Mechanical properties of metallic biomaterials compared to human cortical bone [231–234].

Material	Elastic Modulus (GPa)	Tensile Strength (MPa)	Compressive Strength (MPa)
Cortical bone	3–20	107	130–180
Stainless steel	180–210	700	170–1000
Co-Cr-Mo alloys	230	500	450–1000
Titanium alloys	55–110	950	110–117
Magnesium alloys	41–45	135–285	65–100
Porous Tantalum	2.5–3.9	63	60–78

3.6. Metal augments

Metal augments are structures that can fill severe cavity defects, and thus eliminate the requirement for extensive bone grafting [248]. They can be attached to the underside of tibial implants for segmental defects up to 20 mm in depth [249]. The use of metal augments to treat bone loss has become more popular since it was shown that biomechanically modular augments were suitable for both femoral and tibial defects, especially when metaphyseal bone cannot support the implants (AORI type-2 or -3 defects) or provide enough surface for fixation through PMMA application [10,236,250]. Metal augments can be custom-fabricated using parameters measured on computed tomography (CT), which allows the surgeon performing rTKA to restore the anatomic joint line, correct limb alignment and shorten operative times [251]. Moreover, augments do not need to be incorporated into host bone, so there is no risk of disease transmission, nonunion, shrinkage and collapse [252,253]. Finally, metal augments can facilitate immediate mobilization and load bearing [248].

Metal augments can be made from both tantalum (Ta) and titanium (Ti) because they are biocompatible and osteoconductive [254,255]. Furthermore, they have thrombogenic potential, promoting blood clots which can aid in bone healing [256]. Metal augments are available in different shapes, including wedges (full and hemi), blocks (rectangular), cones and sleeves (Fig. 2), and they can be attached with cement, screws or a Morse-taper junction [13].

3.6.1. Block and wedge shaped augments

Block and wedge shaped augments can be used for tibial and femoral bone defects up to 10 mm in height. They are used for tibial augmentation to address entire, or localized, bone deficiency of the plateau. Preference between the wedges and blocks depends on the position and shape of the defect; with femoral bone deficiency, block shaped augments with variable thickness are preferred [259]. Studies have also shown that block augments have a lower rate of implant loosening, and that they are more stable than wedges, due to the lower induced shear forces [260]. Furthermore, when a constrained insert is

Table 15
Summary of the clinical findings after using megaprostheses in rTKAs.

	Number of cases (knees)	Infection	Fracture	Aseptic loosening	Others	Follow-ups (months)
Springer *et al.* [244]	22 revisions, 4 primary procedures	5	1 fracture of the axis	0	1 delayed wound healing 1 fracture of patella	Average follow-up 58.5
Back *et al.* [245]	32	3	0	1	6% patellofemoral complications	54-132
Berend *et al.* [246]	39	3	1 periprosthetic fracture	0	1 hyperextension	24–109
Höll *et al.* [243]	21	5 periprosthetic infection	9	2	5 nonunions	10–18
Vertesich *et al.* [247]	30	8	NA[a]	4	3 soft tissue complications 1 structural failure	120

[a] Not available.

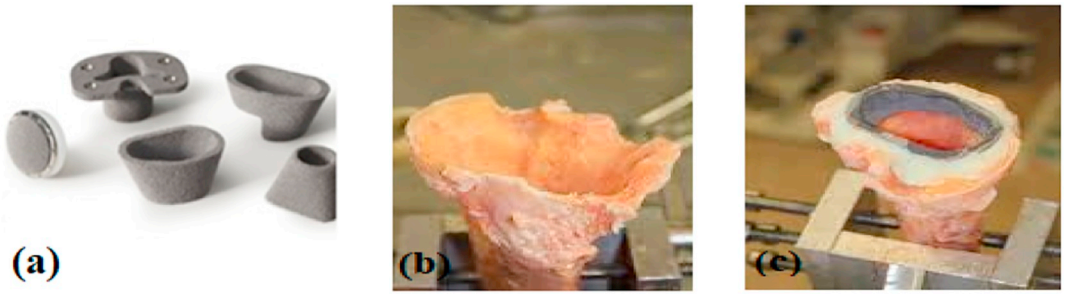

Fig. 2. (a) Zimmer® Trabecular Metal™ cone augments; (b, c) reconstruction of bone loss using porous tantalum augment [257]. Figures b and c were used with permission from Meijer *et al.* [258].

Table 16
Overview of the clinical findings after using porous tantalum cones for rTKAs.

	Numbers	Follow-ups (months)	Loosening	Periprosthetic fracture	Infection	Osseointegration
Meneghini *et al.* [238]	15 tibial cones	34 (24–47)	0	0	0	Yes
Long *et al.* [239]	16 tibial cones	31 (24–38)	0	0	2	Yes
Kamath *et al.* [264]	66 tibial cones	70 (60–106)	1	1	1	no
Potter *et al.* [266]	157 femoral cones	60 (24-120)	6 aseptic loosening 1 ligamentous loosening	0	14	Yes
Burastero *et al.* [267]	97 femoral and/or tibial cones	60	0	0	2	Yes

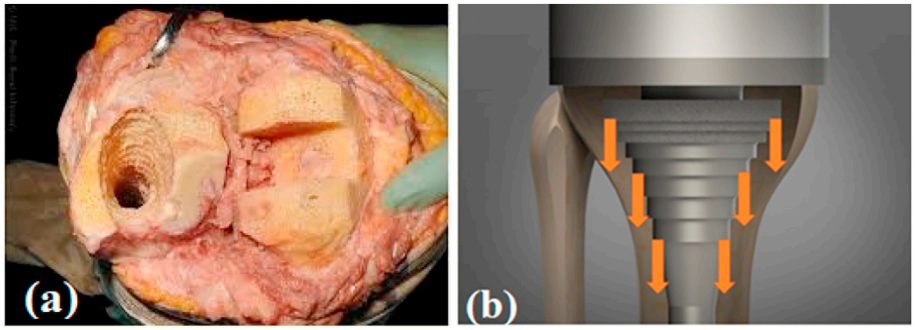

Fig. 3. (a) prepared bone for metaphyseal sleeve insertion. Figure (a) used with the permission from Bugler *et al.* [272] (b) metaphyseal sleeve optimizes load transfer and improves bone regrowth (Wolff's law). The arrows show load directions. Adapted from Agarwal *et al.* [271].

necessary, blocks are preferred as they can transmit torsional loads because of geometric interlock. However, using blocks necessitates the removal of some intact tissues [252].

3.6.2. Porous tantalum metaphyseal cones

Metaphyseal cones have been used for rTKA for a decade [259]. Ta cones have low stiffness with 75–80% porosity and a high coefficient of friction which provides good primary implant stability [251]. Moreover, they are bioactive [254], promoting human osteoblast-like cells [261], corrosion resistant [262] and their modulus of elasticity is similar to human bone [237,252]. Ta surfaces have also been reported to reduce bacterial adhesion [263]. The high porosity of Ta allows the restoration of bone stock by promoting osseointegration [259]. Ta cones are available in different sizes and they can have symmetrical or stepped shapes [250]. Cones connect to implants either by cementation or a press-fit [264], and the voids between the cones and the host tissues are filled with autograft, allograft or graft substitute [18]. However, cones have disadvantages including:

1) the cemented interface between cone and the implant is a common failure site, and can inhibit bone ingrowth across the augment [265];

2) intra-operative fracture can occur if the augment does not match

Table 17
Overview of the clinical findings after using sleeves for rTKAs.

	Number of knees	Aseptic loosening	Infection	Periprosthetic fracture	Others	Survival rate (%)	Follow-ups (months)
Alexander *et al.* [276] (cementless fixation)	30	0	0	0	7 (end-of-stem pain)	NA[a]	22–52
Barnett *et al.* [277]	36	2	1	0	1 end-of-stem pain	88.9	49
Huang *et al.* [278]	119	2	6	0	NA	NA	42
Thorsell *et al.* [279]	31	0	4	1	1 skin necrosis 1 wound rapture 8 (end of stem pain)	77	60
Wirries *et al.* [280]	47	3	3	NA	NA	87.2	60

[a] Not available.

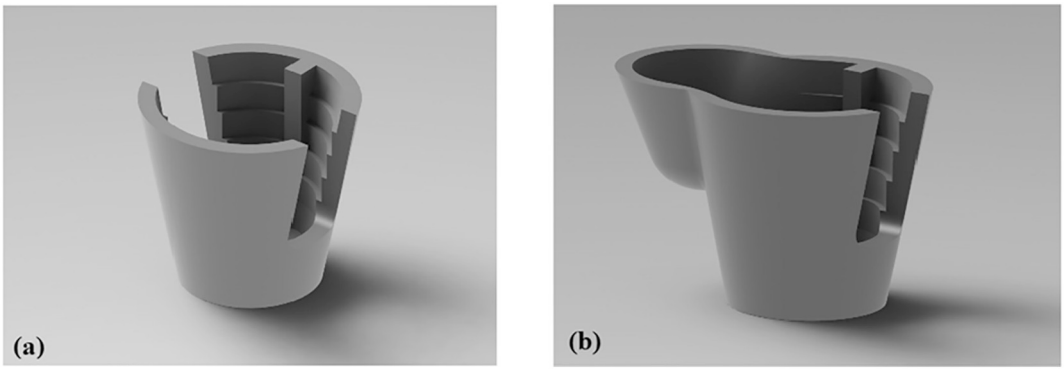

Fig. 4. (a) a symmetric cone (b) an asymmetric cone. Adapted from Faizan *et al.* [284].

the geometry of the prepared bone;

3) removing a well-fixed cone in case of another revision is difficult.

Therefore, Ta cones are not indicated for treating bone deficiency in young patients [18]. Clinical reports for using cones in large bone defects during rTKAs are summarized in Table 16.

3.6.3. Titanium metaphyseal sleeves

The other treatment for type 3 bone defects in rTKAs is the use of metaphyseal sleeves [268]. The sleeve base is made of Ti alloy and coated with Ti beads to produce an interconnected surface with a porosity of 50–80% [269]. The sleeve surface has osseointegrative potential which can provide long-term mechanical support and rotational stability [269]. Sleeves have stepped shapes and they are connected to implants with a Morse-taper junction in cementless fixation [251]. Metaphyseal sleeves can be used for contained, non-contained and irregular defects [270] and are available in various sizes (Fig. 3) [271]. A study showed that prosthesis loosening was far less prevalent in patients with sleeves compared to cones [272]; this can be partially attributed to the increase in bone density due to stimulating collagen and HA synthesis, in line with Wolff's Law [273]. However, the influence of Ti alloy sleeves on the increase of bone formation remains under debate [272,274,275]. Some of the clinical outcomes after using sleeves for rTKAs are shown in Table 17.

Similar to Ta cones, there are some complications related to the use of sleeves, including intra-operative fracture during broaching (enlarging the interior canal of the bone to insert the sleeve) [272], and the difficulty in removal of the sleeves in re-revisions. In addition, sleeves are prosthetic system specific, but cones are not linked to a particular prosthesis [281].

Ti sleeves can be used with or without stems. Stems result in less micromotion and undergo more osseointegration and are therefore more stable than stemless designs [269,282]. However, using stems with sleeves has resulted in pain at the stem tip [269] and increased stress shielding [282]. Furthermore, positioning of the stem is critical [283]. Further study and long-term follow-up are required to indicate the advantages and disadvantages of using metaphyseal sleeves in rTKAs.

3.6.4. 3-D printed Ti cones

Porous Ta metaphyseal cones have high success rates in short and medium-term follow-ups. However, they do not precisely match the metaphyseal area of the tibia and femur, which can offer an intraoperative challenge for surgeons [284]. The geometries for the latest 3-D printed Ti cones, however, are based on patient-specific tibial and femoral morphologies derived from CT scans [284]. The interface between the cone and the implant is filled with PMMA and, as a result, there is no need for bone grafting [281]. Ti cones not only provide mechanical stability similar to Ta cones, but also the bone preparation, extraction and longitudinal fractures during surgery are minimized [284]. Denethy *et al.* used highly porous titanium cones produced from 3-D printed technology in 62 rTKAs surgeries. Revision-free survival for a mean follow-up of 27 months (range 24–34) was 90.2% [285]. 3-D Ti cones can have symmetric (type 1 and 2 bone defects) or asymmetric shapes (lobe shaped – type 3 bone defect) and are adaptable to any implant (Fig. 4) [281]. Asymmetric shapes are used for both tibial and femoral bone defects in rTKA, but symmetric shapes are usually for tibial defects in rTKA [284]. Long-term follow-ups are required to evaluate all the advantages and disadvantages of this novel method.

To summarize, all metal augments (blocks, wedges, hemi wedges, cones, sleeves) have inherent problems, including:

- lack of potential for host bone restoration, causing additional bone loss during both insertion and revision [262],
- metal debris can be released at the time of connection [286],
- further bone resection may be required to obtain suitable fit [262],
- increased risk of fretting and corrosion [286],
- differences in elasticity between the metal augment and bone may cause stress shielding and increase the potential for bone loss [15].
- removal of metal augments in re-revision is difficult [287].

3.7. Bioactive augments

One of the critical factors that causes the low success rates of synthetic grafts and metal augments is their inability to provide adequate osteogenetic, osteoconductive and osteoinductive effects [9]. Thus, a successful augment which provides a three-dimensional structure and also has osteoinductive potential can be a promising treatment for rTKA [7]. Bioactive augments can be used as intermediate phase implants which provide adequate mechanical properties (which are variable in relation to the bone type and load zone) during bone regeneration, and mass transport, including nutrition and waste [288].

Several synthetic bone graft substitutes which have been investigated for the fabrication of augments were discussed in Sections 3.2.2 [289]. However, they are still in the developmental stage and are not ready for clinical use.

4. Conclusions

1. Despite the improvements in biomaterials used to treat bone loss in orthopedics, an ideal alternative to augments in rTKA does not yet exist.

2. Metal augments with highly interconnected porous structures have the potential to revolutionize rTKA, since they can facilitate bone ingrowth and provide good stability. However, they have inherent problems such as wear due to fretting and corrosion, and can cause stress shielding. Furthermore, their large surface area facilitates bacterial adhesion.

3. Developing bioactive augments that have structural integrities, biodegradation, and bone formation rates similar to those of human bone would overcome the drawbacks of metal augments.

4. Bioactive glasses are promising low-cost materials for augmentation since they are both osteoconductive and osteoinductive. Furthermore, the compositional flexibility of bioactive glasses makes it possible to use them as a source of ions to prevent infection and biofilm formation and/or to regulate the augment degradation, and bone formation rate.

The future of bone loss management may lie in the fabrication of bioactive augments that can bring together a construct that restores, maintains and improves damaged tissues. This construct could replace metal-based augments and revolutionize bone loss treatment methods.

Acknowledgment

The authors would like to thank CIHR/NSERC-Collaborative Health Research Projects (356780-DAN) for the financial support.

References

[1] G. Labek, M. Thaler, W. Janda, M. Agreiter, B. Stöckl, Revision rates after total joint replacement: cumulative results from worldwide joint register datasets, J. Bone Joint Surg. 93 (2011) 293–297.
[2] C.J. Lavernia, M.K. Drakeford, A.K. Tsao, A. Gittelsohn, K.A. Krackow, D.S. Hungerford, Revision and primary hip and knee arthroplasty: a cost analysis, Clin. Orthop. Relat. Res. 311 (1995) 136–141.
[3] A.C. de Waal Malefijt, A. van Kampen, T.J. Slooff, Bone grafting in cemented knee replacement: 45 primary and secondary cases followed for 2-5 years, Acta Orthop. Scand. 66 (1995) 325–328.
[4] D. Ruiz, L. Koenig, T.M. Dall, P. Gallo, A. Narzikul, J. Parvizi, et al., The direct and indirect costs to society of treatment for end-stage knee osteoarthritis, The journal of bone joint surgery 95 (2013) 1473–1480.
[5] J.L. Bush, J.B. Wilson, T.P. Vail, Management of bone loss in revision total knee arthroplasty, Clin. Orthop. Relat. Res. 452 (2006) 186–192.
[6] J. Whittaker, R. Dharmarajan, A. Toms, The management of bone loss in revision total knee replacement, Bone & joint journal 90 (2008) 981–987.
[7] L. Polo-Corrales, M. Latorre-Esteves, J.E. Ramirez-Vick, Scaffold design for bone regeneration, J. Nanosci. Nanotechnol. 14 (2014) 15–56.
[8] K.J. Burg, S. Porter, J.F. Kellam, Biomaterial developments for bone tissue engineering, Biomaterials 21 (2000) 2347–2359.
[9] C. Laurencin, Y. Khan, S.F. El-Amin, Bone graft substitutes, Expert review of medical devices 3 (2006) 49–57.
[10] C.S. Radnay, G.R. Scuderi, Management of bone loss: augments, cones, offset stems, Clin. Orthop. Relat. Res. 446 (2006) 83–92.
[11] P. Burdin, S. Lautman, J. Brilhault, Bone loss with total knee replacement, Osteoarthritis of the Knee, 2008, p. 395.
[12] D. Dan, D. Germann, H. Burki, P. Hausner, U. Kappeler, R.P. Meyer, et al., Bone loss after total hip arthroplasty, Rheumatol. Int. 26 (2006) 792–798.
[13] G. Panegrossi, M. Ceretti, M. Papalia, F. Casella, F. Favetti, F. Falez, Bone loss management in total knee revision surgery, Int. Orthop. 38 (2014) 419–427.
[14] Y.Y. Qiu, C.H. Yan, K.Y. Chiu, F.Y. Ng, Bone defect classifications in revision total knee arthroplasty, J. Orthop. Surg. 19 (2011) 238–243.
[15] Y.Y. Qiu, C.H. Yan, K.Y. Chiu, F.Y. Ng, Review article: treatments for bone loss in revision total knee arthroplasty, J. Orthop. Surg. 20 (2012) 78.
[16] D. Backstein, O. Safir, A. Gross, Management of bone loss: structural grafts in revision total knee arthroplasty, Clin. Orthop. Relat. Res. 446 (2006) 104–112.
[17] R.A. Kuchinad, S. Garbedian, B.A. Rogers, D. Backstein, O. Safir, A.E. Gross, The use of structural allograft in primary and revision knee arthroplasty with bone loss, Advances in orthopedics 2011 (2011).
[18] F. Mancuso, A. Beltrame, E. Colombo, E. Miani, F. Bassini, Management of metaphyseal bone loss in revision knee arthroplasty, Acta bio medica atenei parmensis 88 (2017) 98–111.
[19] K.J. Mulhall, H.M. Ghomrawi, G.A. Engh, C.R. Clark, P. Lotke, K.J. Saleh, Radiographic prediction of intraoperative bone loss in knee arthroplasty revision, Clin. Orthop. Relat. Res. 446 (2006) 51–58.
[20] G.A. Engh, Classification of bone defects femur and tibia, Knee Arthroplasty Handbook, 2006, pp. 116–132.
[21] J.R. Pécora, B.B. Hinckel, M.K. Demange, R.G. Gobbi, L.E.P. Tirico, M.M. Iamaguchi, Interobserver correlation in classification of bone loss in total knee arthroplasty, Acta Ortopédica Brasileira 19 (2011) 368–372.
[22] J. Compston, Bone quality: what is it and how is it measured? Arquivos brasileiros de endocrinologia & metabologia 50 (2006) 579–585.
[23] P.V. Giannoudis, H. Dinopoulos, E. Tsiridis, Bone substitutes: an update, Injury 36 (2005) S20–S27.
[24] T.J. Cypher, J.P. Grossman, Biological principles of bone graft healing, The Journal of foot and ankle surgery 35 (1996) 413–417.
[25] C.G. Finkemeier, Bone-grafting and bone-graft substitutes, JBJS 84 (2002) 454–464.
[26] E.E. Keller, W.W. Triplett, Iliac bone grafting: review of 160 consecutive cases, J. Oral Maxillofac. Surg. 45 (1987) 11–14.
[27] G.A. Catone, B.L. Reimer, D. McNeir, R. Ray, Tibial autogenous cancellous bone as an alternative donor site in maxillofacial surgery: a preliminary report, J. Oral Maxillofac. Surg. 50 (1992) 1258–1263.
[28] J.O. Krause, C.R. Perry, Distal femur as a donor site of autogenous cancellous bone graft, J. Orthop. Trauma 9 (1995) 145–151.
[29] M.V. Belthur, J.D. Conway, G. Jindal, A. Ranade, J.E. Herzenberg, Bone graft harvest using a new intramedullary system, Clin. Orthop. Relat. Res. 466 (2008) 2973–2980.
[30] N.A. Ebraheim, H. Elgafy, R. Xu, Bone graft harvesting from iliac and fibular donor sites: techniques and complications, J. Am. Acad. Orthop. Surg. 9 (2001) 210–218.
[31] R.R. Betz, Limitations of autograft and allograft: new synthetic solutions, Orthopedics 25 (2002) S561–S570.
[32] H. Nguyen, D.A. Morgan, M.R. Forwood, Sterilization of allograft bone: effects of gamma irradiation on allograft biology and biomechanics, Cell Tissue Bank. 8 (2007) 93–105.
[33] J. Henkel, M.A. Woodruff, D.R. Epari, R. Steck, V. Glatt, I.C. Dickinson, et al., Bone regeneration based on tissue engineering conceptions—a 21st century perspective, Bone research 1 (2013) 216.
[34] V. Campana, G. Milano, E. Pagano, M. Barba, C. Cicione, G. Salonna, et al., Bone substitutes in orthopaedic surgery: from basic science to clinical practice, J. Mater. Sci. Mater. Med. 25 (2014) 2445–2461.
[35] S. Nandi, S. Roy, P. Mukherjee, B. Kundu, D. De, D. Basu, Orthopaedic Applications of Bone Graft & Graft Substitutes: A Review, (2010).
[36] L.F. Bush, The use of homogenous bone grafts: a preliminary report on the bone bank, JBJS 29 (1947) 620–628.
[37] J. Chalmers, Transplantation immunity in bone homografting, Bone & joint journal 41 (1959) 160–179.
[38] V. Grover, A. Kapoor, R. Malhotra, S. Sachdeva, Bone allografts: a review of safety and efficacy, Indian J. Dent. Res. 22 (2011) 496.
[39] W. Wang, K.W. Yeung, Bone grafts and biomaterials substitutes for bone defect repair: a review, Bioactive materials 2 (2017) 224–247.
[40] A.H. Reddi, A. Reddi, Bone morphogenetic proteins (BMPs): from morphogens to metabologens, Cytokine Growth Factor Rev. 20 (2009) 341–342.
[41] R. Maatz, The animal bone chip in the bone bank, Deutsches medizinisches Journal 8 (1957) 190.
[42] P. Mathias, D.A. Seigerman, The clinical use of allografts, demineralized bone matrices, synthetic bone graft substitutes and osteoinductive growth factors: a survey study, HSS journal; the musculoskeletal journal of hospital for special surgery 1 (2005) 9.
[43] S.N. Khan, F.P. Cammisa Jr., H.S. Sandhu, A.D. Diwan, F.P. Girardi, J.M. Lane, The biology of bone grafting, JAAOS-Journal of the American Academy of Orthopaedic Surgeons 13 (2005) 77–86.
[44] V.Y. Ng, Risk of disease transmission with bone allograft, Orthopedics 35 (2012) 679–681.
[45] W. Mnaymneh, R.H. Emerson, F. Borja, W.C. Head, T.I. Malinin, Massive allografts in salvage revisions of failed total knee arthroplasties, Clin. Orthop. Relat. Res. (1990) 144–153.
[46] M. Clatworthy, J. Ballance, G. Brick, H. Chandler, A. Gross, The use of structural allograft for uncontained defects in revision total knee arthroplasty: a minimum

five-year review, JBJS 83 (2001) 404–411.
[47] G.A. Engh, D.J. Ammeen, Use of structural allograft in revision total knee arthroplasty in knees with severe tibial bone loss, JBJS 89 (2007) 2640–2647.
[48] W. Steens, J.F. Loehr, J. Wodtke, A. Katzer, Morselized bone grafting in revision arthroplasty of the knee: a retrospective analysis of 34 reconstructions after 2–9 years, Acta Orthop. 79 (2008) 683–688.
[49] R. Malhotra, B. Garg, V. Kumar, Dual massive skeletal allograft in revision total knee arthroplasty, Indian journal of orthopaedics 45 (2011) 368.
[50] S.-H. Lee, S.-H. Noh, K.-C. Chun, J.-K. Han, C.-H. Chun, A case of bilateral revision total knee arthroplasty using distal femoral allograft–prosthesis composite and femoral head allografting at the tibial site with a varus-valgus constrained prosthesis: ten-year follow up, BMC Musculoskelet. Disord. 19 (2018) 69.
[51] H.J. Mankin, F.J. Hornicek, K.A. Raskin, Infection in massive bone allografts, Clin. Orthop. Relat. Res. (432) (2005) 210–216.
[52] F. Kwong, T. Ibrahim, R. Power, Incidence of infection with the use of non-irradiated morcellised allograft bone washed at the time of revision arthroplasty of the hip, Bone & joint journal 87 (2005) 1524–1526.
[53] G. Guillemin, A. Meunier, P. Dallant, P. Christel, J.C. Pouliquen, L. Sedel, Comparison of coral resorption and bone apposition with two natural corals of different porosities, J. Biomed. Mater. Res. A 23 (1989) 765–779.
[54] R. Maatz, A. Bauermeister, A method of bone maceration: results in animal experiments, JBJS 39 (1957) 153–166.
[55] C.V. Diesel, T.A. Ribeiro, M.R. Guimarães, C.A.d.S. Macedo, C.R. Galia, Acetabular revision in total hip arthroplasty with tantalum augmentation and lyophilized bovine xenograft, Rev. Bras. Ortop. 52 (2017) 46–51.
[56] C. Charalambides, M. Beer, A.G. Cobb, Poor results after augmenting autograft with xenograft (Surgibone) in hip revision surgery: a report of 27 cases, Acta Orthop. 76 (2005) 544–549.
[57] H. Burchardt, The biology of bone graft repair, Clin. Orthop. Relat. Res. 174 (1983) 28–34.
[58] S. Louisia, M. Stromboni, A. Meunier, L. Sedel, H. Petite, Coral grafting supplemented with bone marrow, Journal of bone & joint Surgery 81 (1999) 719–724.
[59] O. Schwartz and I. Binderman, "Coral bone graft substitute," US Patent, 2015.
[60] C. Demers, C.R. Hamdy, K. Corsi, F. Chellat, M. Tabrizian, L.H. Yahia, Natural coral exoskeleton as a bone graft substitute: a review, Biomed. Mater. Eng. 12 (2002) 15–35.
[61] J.A. Chamberlain, Mechanical properties of coral skeleton: compressive strength and its adaptive significance, Paleobiology 4 (2016) 419–435.
[62] A. Nicolaides, A. Papanikolaou, A. Polyzoides, Successful treatment of valgus deformity of the knee with an open supracondylar osteotomy using a coral wedge: a brief report of two cases, Knee 7 (2000) 105–107.
[63] D.R. Jordan, S. Gilberg, L. Mawn, S. Brownstein, S.Z. Grahovac, The synthetic hydroxyapatite implant: a report on 65 patients, Ophthal. Plast. Reconstr. Surg. 14 (1998) 250–255.
[64] S.W. Wolfe, L. Pike, J.F. Slade III, L.D. Katz, Augmentation of distal radius fracture fixation with coralline hydroxyapatite bone graft substitute, The Journal of hand surgery 24 (1999) 816–827.
[65] G.S. Krishnakumar, A. Roffi, D. Reale, E. Kon, G. Filardo, Clinical application of bone morphogenetic proteins for bone healing: a systematic review, Int. Orthop. 41 (2017) 1073–1083.
[66] G.E. Friedlaender, C.R. Perry, J.D. Cole, S.D. Cook, G. Cierny, G.F. Muschler, et al., Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions: a prospective, randomized clinical trial comparing rhOP-1 with fresh bone autograft, JBJS 83 (2001) S151.
[67] S. Govender, C. Csimma, H.K. Genant, A. Valentin-Opran, Y. Amit, R. Arbel, et al., Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients, JBJS 84 (2002) 2123–2134.
[68] C.R. Bragdon, A.M. Doherty, H.E. Rubash, M. Jasty, X.J. Li, H. Seeherman, et al., The John Charnley award: the efficacy of BMP-2 to induce bone ingrowth in a total hip replacement model, Clin. Orthop. Relat. Res. 417 (2003) 50–61.
[69] R. Geesink, N. Hoefnagels, S. Bulstra, Osteogenic activity of OP-1 bone morphogenetic protein (BMP-7) in a human fibular defect, The Journal of bone and joint surgery. British volume 81 (1999) 710–718.
[70] M. Jäger, R. Emami, F. Thorey, R. Krauspe, Saving implants BMP-2 application in revision total hip surgery, International journal of biomedical science: IJBS 2 (2006) 187.
[71] K.W.-H. Lo, B.D. Ulery, K.M. Ashe, C.T. Laurencin, Studies of bone morphogenetic protein-based surgical repair, Adv. Drug Deliv. Rev. 64 (2012) 1277–1291.
[72] L.C. Gerstenfeld, D.M. Cullinane, G.L. Barnes, D.T. Graves, T.A. Einhorn, Fracture healing as a post-natal developmental process: molecular, spatial, and temporal aspects of its regulation, J. Cell. Biochem. 88 (2003) 873–884.
[73] P.V. Giannoudis, S. Psarakis, N.K. Kanakaris, H.-C. Pape, Biological enhancement of bone healing with bone morphogenetic protein-7 at the clinical setting of pelvic girdle non-unions, Injury 38 (2007) S43–S48.
[74] L.V. Gressot, A.J. Patel, S.W. Hwang, D.H. Fulkerson, A. Jea, Rh-BMP-2 for L5–S1 arthrodesis in long fusions to the pelvis for neuromuscular spinal deformity in the pediatric age group: analysis of 11 patients, Childs Nerv. Syst. 30 (2014) 249–255, https://doi.org/10.1007/s00381-013-2221-6.
[75] A.L. Jones, R.W. Bucholz, M.J. Bosse, S.K. Mirza, T.R. Lyon, L.X. Webb, et al., Recombinant human BMP-2 and allograft compared with autogenous bone graft for reconstruction of diaphyseal tibial fractures with cortical defects, The journal of bone & joint surgery 88 (2006) 1431–1441.
[76] M.F. Swiontkowski, H.T. Aro, S. Donell, J.L. Esterhai, J. Goulet, A. Jones, et al., Recombinant human bone morphogenetic protein-2 in open tibial fractures: a subgroup analysis of data combined from two prospective randomized studies, JBJS 88 (2006) 1258–1265.
[77] G. Zimmermann, C. Wagner, K. Schmeckenbecher, A. Wentzensen, A. Moghaddam, Treatment of tibial shaft non-unions: bone morphogenetic proteins versus autologous bone graft, Injury 40 (2009) S50–S53.
[78] P.V. Giannoudis, N.K. Kanakaris, R. DimitriouIan, G. Kolimarala, R.J. Montgomery, The synergistic effect of autograft and BMP-7 in the treatment of atrophic nonunions, Clin. Orthop. Relat. Res. 467 (2009) 3239–3248.
[79] P.P. Desai, A.J. Bell, M. Suk, Treatment of recalcitrant, multiply operated tibial nonunions with the RIA graft and rh-BMP2 using intramedullary nails, Injury 41 (2010) S69–S71.
[80] J.D. Conway, L. Shabtai, A. Bauernschub, S.C. Specht, BMP-7 versus BMP-2 for the treatment of long bone nonunion, Orthopedics 37 (2014) e1049–e1057.
[81] W. Sun, Z. Li, F. Gao, Z. Shi, Q. Zhang, W. Guo, Recombinant human bone morphogenetic protein-2 in debridement and impacted bone graft for the treatment of femoral head osteonecrosis, PLoS One 9 (2014) e100424.
[82] A.W. James, G. LaChaud, J. Shen, G. Asatrian, V. Nguyen, X. Zhang, et al., A review of the clinical side effects of bone morphogenetic protein-2, Tissue Eng. B Rev. 22 (2016) 284–297.
[83] K. Hata, R. Nishimura, F. Ikeda, K. Yamashita, T. Matsubara, T. Nokubi, et al., Differential roles of Smad1 and p38 kinase in regulation of peroxisome proliferator-activating receptor γ during bone morphogenetic protein 2-induced adipogenesis, Mol. Biol. Cell 14 (2003) 545–555.
[84] R. Huang, Y. Yuan, J. Tu, G. Zou, Q. Li, Opposing TNF-α/IL-1β-and BMP-2-activated MAPK signaling pathways converge on Runx2 to regulate BMP-2-induced osteoblastic differentiation, Cell Death Dis. 5 (2014) e1187.
[85] L.L. Hench, J.M. Polak, Third-generation biomedical materials, Science 295 (2002) 1014–1017.
[86] M. Navarro, A. Michiardi, O. Castano, J. Planell, Biomaterials in orthopaedics, J. R. Soc. Interface 5 (2008) 1137–1158.
[87] L.L. Hench, Ö. Andersson, Bioactive glasses, An Introduction to Bioceramics, World Scientific, 1993, pp. 41–62.
[88] A.R. Vaccaro, The role of the osteoconductive scaffold in synthetic bone graft, Orthopedics 25 (2002) S571–S578.
[89] W.R. Moore, S.E. Graves, G.I. Bain, Synthetic bone graft substitutes, ANZ J. Surg. 71 (2001) 354–361.
[90] S. Stevenson, S.E. Emery, V.M. Goldberg, Factors affecting bone graft incorporation, Clin. Orthop. Relat. Res. 324 (1996) 66–74.
[91] G. Zimmermann, A. Moghaddam, Allograft bone matrix versus synthetic bone graft substitutes, Injury 42 (2011) S16–S21.
[92] D.G. Poitout, Biomechanics and Biomaterials in Orthopedics, (2004).
[93] An Introduction to Bioceramics, second edition, Imperial College Press, 2013.
[94] R. Doremus, Bioceramics, J. Mater. Sci. 27 (1992) 285–297.
[95] F. Baino, G. Novajra, C. Vitale-Brovarone, Bioceramics and scaffolds: a winning combination for tissue engineering, Frontiers in bioengineering and biotechnology 3 (2015) 202.
[96] P. Hernigou, Plaster of Paris: the orthopaedic surgeon heritage, Int. Orthop. 40 (2016) 1767–1779.
[97] B.K. Tay, V.V. Patel, D.S. Bradford, Calcium sulfate–and calcium phosphate–based bone substitutes, Orthopedic clinics 30 (1999) 615–623.
[98] C.M. Kelly, R.M. Wilkins, S. Gitelis, C. Hartjen, J.T. Watson, P.T. Kim, The use of a surgical grade calcium sulfate as a bone graft substitute: results of a multicenter trial, Clin. Orthop. Relat. Res. 382 (2001) 42–50.
[99] R. Kallala, W.E. Harris, M. Ibrahim, M. Dipane, E. McPherson, Use of Stimulan absorbable calcium sulphate beads in revision lower limb arthroplasty: safety profile and complication rates, Bone & joint research 7 (2018) 570–579.
[100] W. Walsh, P. Morberg, Y. Yu, J.L. Yang, W. Haggard, P. Sheath, et al., Response of a calcium sulfate bone graft substitute in a confined cancellous defect, Clin. Orthop. Relat. Res. 406 (2003) 228–236.
[101] T.T. Roberts, A.J. Rosenbaum, Bone grafts, bone substitutes and orthobiologics: the bridge between basic science and clinical advancements in fracture healing, Organogenesis 8 (2012) 114–124.
[102] A.S. Coetzee, Regeneration of bone in the presence of calcium sulfate, Arch. Otolaryngol. 106 (1980) 405–409.
[103] D.J. Hak, The use of osteoconductive bone graft substitutes in orthopaedic trauma, J. Am. Acad. Orthop. Surg. 15 (2007) 525–536.
[104] D.A. Corral, M. Amling, M. Priemel, E. Loyer, S. Fuchs, P. Ducy, et al., Dissociation between bone resorption and bone formation in osteopenic transgenic mice, Proc. Natl. Acad. Sci. 95 (1998) 13835–13840.
[105] C. Yashavantha Kumar, K. Nalini, D.K.P. Jagdish Menon, B. Banerji, Calcium sulfate as bone graft substitute in the treatment of osseous bone defects, a prospective study, J. Clin. Diagn. Res. 7 (2013) 2926.
[106] L.F. Peltier, R.H. Jones, Treatment of unicameral bone cysts by curettage and packing with plaster-of-Paris pellets, Clin. Orthop. Relat. Res. 422 (2004) 145–147.
[107] R. LeGeros, S. Lin, R. Rohanizadeh, D. Mijares, J. LeGeros, Biphasic calcium phosphate bioceramics: preparation, properties and applications, J. Mater. Sci. Mater. Med. 14 (2003) 201–209.
[108] E. Monroe, W. Votava, D. Bass, J.M. Mullen, New calcium phosphate ceramic material for bone and tooth implants, J. Dent. Res. 50 (1971) 860–861.
[109] H. S. Cheung and M. H. Haak, "Growth of osteoblasts on porous calcium phosphate ceramic: an in vitro model for biocompatibility study," Biomaterials, vol. 10, pp. 63–67, (1989/01/01/ 1989).
[110] R.Z. LeGeros, Properties of osteoconductive biomaterials: calcium phosphates, Clin. Orthop. Relat. Res. 395 (2002) 81–98.
[111] C. Klein, A. Driessen, K. De Groot, A. Van Den Hooff, Biodegradation behavior of various calcium phosphate materials in bone tissue, J. Biomed. Mater. Res. A 17

(1983) 769–784.
[112] J. Toquet, R. Rohanizadeh, J. Guicheux, S. Couillaud, N. Passuti, G. Daculsi, et al., Osteogenic potential in vitro of human bone marrow cells cultured on macroporous biphasic calcium phosphate ceramic, Journal of Biomedical Materials Research: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and the Australian Society for Biomaterials 44 (1999) 98–108.
[113] M. Akao, N. Miura, H. Aoki, Fracture toughness of sintered hydroxyapatite and BETA.-tricalcium phosphate, Journal of the ceramic association, Japan 92 (1984) 672–674.
[114] K.S. Lau, A. Nurazreena, Effect of sintering temperature on the Diametral tensile strength of β-tricalcium phosphate block, Advanced Materials Research, 2014, pp. 312–315.
[115] R. Martin, P. Brown, Mechanical properties of hydroxyapatite formed at physiological temperature, J. Mater. Sci. Mater. Med. 6 (1995) 138–143.
[116] S. Kobayashi, W. Kawai, S. Wakayama, The effect of pressure during sintering on the strength and the fracture toughness of hydroxyapatite ceramics, J. Mater. Sci. Mater. Med. 17 (2006) 1089–1093.
[117] V. Karageorgiou, D. Kaplan, Porosity of 3D biomaterial scaffolds and osteogenesis, Biomaterials 26 (2005) 5474–5491.
[118] L.-C. Gerhardt, A.R. Boccaccini, Bioactive glass and glass-ceramic scaffolds for bone tissue engineering, Materials 3 (2010) 3867–3910.
[119] R.W. Bucholz, A. Carlton, R. Holmes, Interporous hydroxyapatite as a bone graft substitute in tibial plateau fractures, Clin. Orthop. Relat. Res. 240 (1989) 53–62.
[120] L. Sun, C.C. Berndt, K.A. Gross, A. Kucuk, Material fundamentals and clinical performance of plasma-sprayed hydroxyapatite coatings: a review, J. Biomed. Mater. Res. A 58 (2001) 570–592.
[121] M.P. McAndrew, P.W. Gorman, T.A. Lange, Tricalcium phosphate as a bone graft substitute in trauma: preliminary report, J. Orthop. Trauma 2 (1988) 333–339.
[122] Y.J. Chen, J.L. Pao, C.S. Chen, Y.C. Chen, C.C. Chang, F.M. Hung, et al., Evaluation of new biphasic calcium phosphate bone substitute: rabbit femur defect model and preliminary clinical results, Journal of medical and biological engineering 37 (2017) 85–93.
[123] A. El-Ghannam, Bone reconstruction: from bioceramics to tissue engineering, Expert review of medical devices 2 (2005) 87–101.
[124] L. Hench, H. Paschall, Histochemical responses at a biomaterial's interface, J. Biomed. Mater. Res. A 8 (1974) 49–64.
[125] L.L. Hench, The story of bioglass®, J. Mater. Sci. Mater. Med. 17 (2006) 967–978.
[126] P. Ducheyne, Q. Qiu, Bioactive ceramics: the effect of surface reactivity on bone formation and bone cell function, Biomaterials 20 (1999) 2287–2303.
[127] L.L. Hench, J. Wilson, Surface-active biomaterials, Science 226 (1984) 630–636.
[128] Q. Chen, J. Roether, A. Boccaccini, Topics in Tissue Engineering, vol. 4, (2008).
[129] T. Graham, Researches on the arseniates, phosphates, and modifications of phosphoric acid, Philos. Trans. R. Soc. Lond. 123 (1833) 253–284.
[130] N. Sharmin, F. Gu, I. Ahmed, A.J. Parsons, Compositional dependency on dissolution rate and cytocompatibility of phosphate-based glasses: effect of B2O3 and Fe2O3 addition, Journal of tissue engineering 8 (2017) 2041731417744454.
[131] C. Tan, I. Ahmed, A.J. Parsons, N. Sharmin, C. Zhu, J. Liu, et al., Structural, thermal and dissolution properties of MgO-and CaO-containing borophosphate glasses: effect of Fe2O3 addition, J. Mater. Sci. 52 (2017) 7489–7502.
[132] S.P. Valappil, D.M. Pickup, D.L. Carroll, C.K. Hope, J. Pratten, R.J. Newport, et al., Effect of silver content on the structure and antibacterial activity of silver-doped phosphate-based glasses, Antimicrob. Agents Chemother. 51 (2007) 4453–4461.
[133] K. Franks, I. Abrahams, J. Knowles, Development of soluble glasses for biomedical use part I: in vitro solubility measurement, J. Mater. Sci. Mater. Med. 11 (2000) 609–614.
[134] V. Salih, K. Franks, M. James, G. Hastings, J. Knowles, I. Olsen, Development of soluble glasses for biomedical use part II: the biological response of human osteoblast cell lines to phosphate-based soluble glasses, J. Mater. Sci. Mater. Med. 11 (2000) 615–620.
[135] B. Bunker, G. Arnold, J.A. Wilder, Phosphate glass dissolution in aqueous solutions, J. Non-Cryst. Solids 64 (1984) 291–316.
[136] H. Gao, T. Tan, D. Wang, Dissolution mechanism and release kinetics of phosphate controlled release glasses in aqueous medium, J. Control. Release 96 (2004) 29–36.
[137] C. Vitale-Brovarone, E. Verné, F. Baino, G. Ciapetti, E. Leonardi, N. Baldini, Bioresorbable phosphate scaffolds for bone regeneration, Key Engineering Materials, 2008, pp. 241–244.
[138] M. Navarro, S. del Valle, S. Martínez, S. Zeppetelli, L. Ambrosio, J.A. Planell, et al., New macroporous calcium phosphate glass ceramic for guided bone regeneration, Biomaterials 25 (2004) 4233–4241.
[139] H. Ylänen, Bioactive Glasses: Materials, Properties and Applications, Woodhead publishing, 2017.
[140] R.W. Cahn, M.C. Flemings, L.L. Hench, B. Ilschner, K.H. Jürgen, E.J. Kramer, et al., Bioglass and similar materials, Encyclopedia of Materials: Science and Technology, *second edition*, Elsevier, Oxford, 2001, pp. 563–568.
[141] Q. Fu, E. Saiz, M.N. Rahaman, A.P. Tomsia, Bioactive glass scaffolds for bone tissue engineering: state of the art and future perspectives, Mater. Sci. Eng. C 31 (2011) 1245–1256.
[142] H. Pirayesh, J.A. Nychka, Sol–gel synthesis of bioactive glass-ceramic 45s5 and its in vitro dissolution and mineralization behavior, J. Am. Ceram. Soc. 96 (2013) 1643–1650.
[143] W. Cao, L.L. Hench, Bioactive materials, Ceram. Int. 22 (1996) 493–507.
[144] M.N. Rahaman, D.E. Day, B.S. Bal, Q. Fu, S.B. Jung, L.F. Bonewald, et al., Bioactive glass in tissue engineering, Acta Biomater. 7 (2011) 2355–2373.
[145] E.G. Kalaf, K. Hixon, P. Kadakia, A. Dunn, S. Sell, Electrospun biomaterials for dermal regeneration, Electrospun Materials for Tissue Engineering and Biomedical Applications, Elsevier, 2017, pp. 179–231.
[146] E. Fiume, J. Barberi, E. Verné, F. Baino, Bioactive glasses: from parent 45S5 composition to scaffold-assisted tissue-healing therapies, Journal of functional biomaterials 9 (2018) 24.
[147] H. Yuan, J.D. de Bruijn, X. Zhang, C.A. van Blitterswijk, K. de Groot, Bone induction by porous glass ceramic made from bioglass®(45S5), Journal of Biomedical Materials Research: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials 58 (2001) 270–276.
[148] X. Zhou, F.M. Moussa, S. Mankoci, P. Ustriyana, N. Zhang, S. Abdelmagid, et al., Orthosilicic acid, Si (OH) 4, stimulates osteoblast differentiation in vitro by upregulating miR-146a to antagonize NF-κB activation, Acta Biomater. 39 (2016) 192–202.
[149] I. Thompson, L. Hench, Mechanical properties of bioactive glasses, glass-ceramics and composites, Proc. Inst. Mech. Eng. H J. Eng. Med. 212 (1998) 127–136.
[150] J.R. Jones, L.M. Ehrenfried, L.L. Hench, Optimising bioactive glass scaffolds for bone tissue engineering, Biomaterials 27 (2006) 964–973.
[151] Q.Z. Chen, I.D. Thompson, A.R. Boccaccini, 45S5 bioglass®-derived glass–ceramic scaffolds for bone tissue engineering, Topics in Tissue Engineering, vol. 27, 2006, pp. 2414–2425.
[152] S. Wu, H. Hsu, S. Hsiao, W. Ho, Preparation of porous 45S5 bioglass®-derived glass–ceramic scaffolds by using rice husk as a porogen additive, J. Mater. Sci. Mater. Med. 20 (2009) 1229–1236.
[153] H. Moawad, H. Jain, Fabrication of nano-macroporous glass–ceramic bioscaffold with a water soluble pore former, J. Mater. Sci. Mater. Med. 23 (2012) 307–314.
[154] S.K. Misra, D. Mohn, T.J. Brunner, W.J. Stark, S.E. Philip, I. Roy, et al., Comparison of nanoscale and microscale bioactive glass on the properties of P (3HB)/bioglass® composites, Biomaterials 29 (2008) 1750–1761.
[155] B. Marelli, C.E. Ghezzi, D. Mohn, W.J. Stark, J.E. Barralet, A.R. Boccaccini, et al., Accelerated mineralization of dense collagen-nano bioactive glass hybrid gels increases scaffold stiffness and regulates osteoblastic function, Biomaterials 32 (2011) 8915–8926.
[156] J. Guan, K.L. Fujimoto, M.S. Sacks, W.R. Wagner, Preparation and characterization of highly porous, biodegradable polyurethane scaffolds for soft tissue applications, Biomaterials 26 (2005) 3961–3971.
[157] Y. Zhou, H. Li, K. Lin, W. Zhai, W. Gu, J. Chang, Effect of heat treatment on the properties of SiO2–CaO–MgO–P2O5 bioactive glasses, J. Mater. Sci. Mater. Med. 23 (2012) 2101–2108.
[158] G.H. Beall, Chain silicate glass-ceramics, J. Non-Cryst. Solids 129 (1991) 163–173.
[159] D. Li, Localized Mechanical Deformation and Dissolution of 45S5 Bioglass, University of Kentucky, 2010.
[160] A.K. Srivastava, R. Pyare, S. Singh, In vitro bioactivity and physical–mechanical properties of MnO2 substituted 45S5 bioactive glasses and glass-ceramics, Journal of biomaterials and tissue engineering 2 (2012) 249–258.
[161] S. Bhakta, D.K. Pattanayak, H. Takadama, T. Kokubo, C.A. Miller, M. Mirsaneh, et al., Prediction of osteoconductive activity of modified potassium fluorrichterite glass-ceramics by immersion in simulated body fluid, J. Mater. Sci. Mater. Med. 21 (2010) 2979–2988.
[162] M. Mirsaneh, I.M. Reaney, P.V. Hatton, P.F. James, Characterization of high-fracture toughness K-Fluorrichterite-Fluorapatite glass ceramics, J. Am. Ceram. Soc. 87 (2004) 240–246.
[163] G.E. Merwin, Bioglass middle ear prosthesis: preliminary report, Annals of Otology, Rhinology & Laryngology 95 (1986) 78–82.
[164] T.B. Lovelace, J.T. Mellonig, R.M. Meffert, A.A. Jones, P.V. Nummikoski, D.L. Cochran, Clinical evaluation of bioactive glass in the treatment of periodontal osseous defects in humans, J. Periodontol. 69 (1998) 1027–1035.
[165] I. Kinnunen, K. Aitasalo, M. Pöllönen, M. Varpula, Reconstruction of orbital floor fractures using bioactive glass, J. Cranio-Maxillofac. Surg. 28 (2000) 229–234.
[166] W. Huang, D.E. Day, K. Kittiratanapiboon, M.N. Rahaman, Kinetics and mechanisms of the conversion of silicate (45S5), borate, and borosilicate glasses to hydroxyapatite in dilute phosphate solutions, J. Mater. Sci. Mater. Med. 17 (2006) 583–596.
[167] A. Yao, D. Wang, W. Huang, Q. Fu, M.N. Rahaman, D.E. Day, In vitro bioactive characteristics of borate-based glasses with controllable degradation behavior, J. Am. Ceram. Soc. 90 (2007) 303–306.
[168] M. Brink, T. Turunen, R.P. Happonen, A. Yli-Urpo, Compositional dependence of bioactivity of glasses in the system Na2O-K2O-MgO-CaO-B2O3-P2O5-SiO2, J. Biomed. Mater. Res. A 37 (1997) 114–121.
[169] Q. Fu, M.N. Rahaman, H. Fu, X. Liu, Silicate, borosilicate, and borate bioactive glass scaffolds with controllable degradation rate for bone tissue engineering applications. I. Preparation and in vitro degradation, J. Biomed. Mater. Res. A 95 (2010) 164–171.
[170] W. Huang, M.N. Rahaman, D.E. Day, Conversion of bioactive silicate (45S5), borate, and borosilicate glasses to hydroxyapatite in dilute phosphate solution, Advances in Bioceramics and Biocomposites II, Ceramic Engineering and Science Proceedings, 2007, pp. 131–140.
[171] L.L. Hench, Biomaterials: a forecast for the future, Biomaterials 19 (1998) 1419–1423.
[172] N.W. Marion, W. Liang, W. Liang, G.C. Reilly, D.E. Day, M.N. Rahaman, et al., Borate glass supports the in vitro osteogenic differentiation of human mesenchymal stem cells, Mech. Adv. Mater. Struct. 12 (2005) 239–246.
[173] H. Fu, Q. Fu, N. Zhou, W. Huang, M.N. Rahaman, D. Wang, et al., In vitro evaluation of borate-based bioactive glass scaffolds prepared by a polymer foam replication method, Mater. Sci. Eng. C 29 (2009) 2275–2281.
[174] Q. Fu, M.N. Rahaman, B.S. Bal, R.F. Brown, D.E. Day, Mechanical and in vitro

performance of 13–93 bioactive glass scaffolds prepared by a polymer foam replication technique, Acta Biomater. 4 (2008) 1854–1864.
[175] W. Huang, M.N. Rahaman, D.E. Day, Y. Li, Mechanisms for converting bioactive silicate, borate, and borosilicate glasses to hydroxyapatite in dilute phosphate solution, Physics and chemistry of glasses part B 47 (2006) 647–658.
[176] M.N. Rahaman, W. Liang, D.E. Day, N.W. Marion, G.C. Reilly, J.J. Mao, Preparation and bioactive characteristics of porous borate glass substrates, Ceramic Engineering and Science Proceedings, 2005, pp. 3–10.
[177] S.B. Jung, D.E. Day, R.F. Brown, L.F. Bonewald, Potential toxicity of bioactive borate glasses in-vitro and in-vivo, Advances in Bioceramics and Porous Ceramics V, 2012, pp. 65–74.
[178] A. Gorustovich, M. Guglielmotti, J. Porto Lopez, R. Cabrini, Increased osteogenesis elicited by boron-modified bioactive glass particles in the SiO2-CaO-P2O5-Na2O system: A histomorphometric study in rats, Key Engineering Materials, 2005, pp. 913–916.
[179] X. Liu, Z. Xie, C. Zhang, H. Pan, M.N. Rahaman, X. Zhang, et al., Bioactive borate glass scaffolds: in vitro and in vivo evaluation for use as a drug delivery system in the treatment of bone infection, J. Mater. Sci. Mater. Med. 21 (2010) 575–582.
[180] Y. Gu, W. Huang, M.N. Rahaman, D.E. Day, Bone regeneration in rat calvarial defects implanted with fibrous scaffolds composed of a mixture of silicate and borate bioactive glasses, Acta Biomater. 9 (2013) 9126–9136.
[181] L. Bi, M.N. Rahaman, D.E. Day, Z. Brown, C. Samujh, X. Liu, et al., Effect of bioactive borate glass microstructure on bone regeneration, angiogenesis, and hydroxyapatite conversion in a rat calvarial defect model, Acta Biomater. 9 (2013) 8015–8026.
[182] H. Wang, S. Zhao, J. Zhou, K. Zhu, X. Cui, W. Huang, et al., Biocompatibility and osteogenic capacity of borosilicate bioactive glass scaffolds loaded with Fe 3 O 4 magnetic nanoparticles, J. Mater. Chem. B 3 (2015) 4377–4387.
[183] K. O'Connell, C. Pierlot, H. O'Shea, D. Beaudry, M. Chagnon, M. Assad, et al., Host responses to a strontium releasing high boron glass using a rabbit bilateral femoral defect model, J. Biomed. Mater. Res. B Appl. Biomater. 105 (2017) 1818–1827.
[184] T. Thamaraiselvi, S. Rajeswari, Biological evaluation of bioceramic materials-a review, Carbon 24 (2004) 172.
[185] L.L. Hench, Bioceramics: from concept to clinic, J. Am. Ceram. Soc. 74 (1991) 1487–1510.
[186] D.G.R.W.D. Callister, Fundamentals of Materials Science and Engineering: An Integrated Approach, (2007).
[187] M.J. Peltola, P.K. Vallittu, V. Vuorinen, A.A.J. Aho, A. Puntala, K.M.J. Aitasalo, Novel composite implant in craniofacial bone reconstruction, Eur. Arch. Otorhinolaryngol. 269 (2012) 623–628.
[188] S. Ramakrishna, J. Mayer, E. Wintermantel, K.W. Leong, Biomedical applications of polymer-composite materials: a review, Compos. Sci. Technol. 61 (2001) 1189–1224.
[189] G.B. Cook, A.W. Walker, E. Schewe, The Cerosium® mandibular prosthesis, Am. J. Surg. 110 (1965) 568–572.
[190] L. Hench, J. Jones, Biomaterials, Artificial Organs and Tissue Engineering, Elsevier, 2005.
[191] A. Daniels, M.K. Chang, K.P. Andriano, J. Heller, Mechanical properties of biodegradable polymers and composites proposed for internal fixation of bone, J. Appl. Biomater. 1 (1990) 57–78.
[192] R.J. Kroeze, M.N. Helder, L.E. Govaert, T.H. Smit, Biodegradable polymers in bone tissue engineering, Materials 2 (2009) 833–856.
[193] C. Chen, H. Wang, F. Smith, G. Glickma, Y. Shyr, R. O'Nea, Evaluation of a collagen membrane with and without bone grafts in treating periodontal intrabony defects, J. Periodontol. 66 (1995) 838–847.
[194] B. Duygu, Ö. Gönen, Ş. Sevda, U. Dilek, U. Ahu, Ö. Ersin, et al., Clinical and radiographic evaluations of chitosan gel in periodontal intraosseous defects: a pilot study, *Journal of biomedical materials research Part B: Applied Biomaterials*, vol (2009) 90B.
[195] G.S. Perrone, G.G. Leisk, T.J. Lo, J.E. Moreau, D.S. Haas, B.J. Papenburg, et al., The use of silk-based devices for fracture fixation, Nat. Commun. 5 (2014) 3385, https://doi.org/10.1038/ncomms4385.
[196] U. Yoshiya, I. Kunio, M. Takamitsu, K. Takahiro, N. Hitoshi, S. Kazuomi, et al., Usefulness as guided bone regeneration membrane of the alginate membrane, Biomaterials 23 (2002).
[197] E. Carlos, A. Maurício, S. Mariana, M. Paulo Antônio, M. Renato de Melo, C. Marcelo Vidigal, et al., Hyaluronic acid accelerates bone repair in human dental sockets: a randomized triple-blind clinical trial, Brazilian oral research 32 (2018).
[198] S. Jun, A. Harold, Biological response of intramedullary bone to poly-L-lactic acid, J. Appl. Biomater. 4 (1993) 13–27.
[199] A.P. Hollander, P.V. Hatton, Biopolymer Methods in Tissue Engineering, vol. 238, Springer, 2004.
[200] K. Rezwan, Q. Chen, J. Blaker, A.R. Boccaccini, Biodegradable and bioactive porous polymer/inorganic composite scaffolds for bone tissue engineering, Biomaterials 27 (2006) 3413–3431.
[201] A. Atala, D.J. Mooney, Synthetic Biodegradable Polymer Scaffolds, (1997).
[202] S. Peter, M.J. Miller, A. Yasko, M.J. Yaszemski, A. Mikos, Polymer concepts in tissue engineering, J. Biomed. Mater. Res. A 43 (1998) 422–427.
[203] R. Vaishya, M. Chauhan, A. Vaish, Bone cement, Journal of Clinical Orthopaedics & Trauma 4 (2013) 157–163.
[204] K.-T. Kwon, K.-Y. Han, W.-S. Lee, D.-H. Kim, Full cementation in revision Total knee arthroplasty using a constrained condylar knee prosthesis with an average 7-year follow-up, Knee surgery & related research 29 (2017) 282.
[205] S. McMahon, G. Hawdon, J. Bare, Y. Sim, N. Bertollo, W.R. Walsh, Thermal necrosis and PMMA- A cause for concern? Orthopaedic Proceedings 94-B (2018) 64.
[206] A. McCaskie, M. Barnes, E. Lin, W. Harper, P. Gregg, Cement pressurisation during hip replacement, J bone & joint surgery 79 (1997) 379–384.
[207] F. MataSSI, C. CarullI, R. Civinini, M. Innocenti, Cemented versus cementless fixation in total knee arthroplasty, Joints 1 (2013) 121.
[208] T. Mumme, R. Marx, M. Qunaibi, F.U. Niethard, D.C. Wirtz, Surface pretreatment for prolonged survival of cemented tibial prosthesis components: full-vs. surface-cementation technique, Biomed Tech (Berl) 51 (2006) 95–102.
[209] J.R. Martin, T.S. Watters, D.L. Levy, J.M. Jennings, D.A. Dennis, Removing a well-fixed femoral sleeve during revision total knee arthroplasty, Arthroplasty today 2 (2016) 171–175.
[210] N. Matsui, Y. Taneda, Y. Yoshida, Arthroplasty 2000: Recent Advances in Total Joint Replacement, (2012).
[211] C.H. Yan, K.Y. Chiu, T.P. Ng, F.Y. Ng, Revision total hip arthroplasty with femoral impaction bone grafting, J. Orthop. Surg. 18 (2010) 303–308.
[212] M.A. Ritter, Screw and cement fixation of large defects in total knee arthroplasty, J. Arthroplast. 1 (1986) 125–129.
[213] M.A. Ritter, E.M. Keating, P.M. Faris, Screw and cement fixation of large defects in total knee arthroplasty: a sequel, J. Arthroplast. 8 (1993) 63–65.
[214] M.E. Berend, M.A. Ritter, E.M. Keating, M.D. Jackson, K.E. Davis, R.A. Malinzak, Use of screws and cement in revision TKA with primary or revision specific prosthesis with up to 17 years followup, J. Arthroplast. 30 (2015) 86–89.
[215] P. Procter, P. Bennani, C. Brown, J. Arnoldi, D. Pioletti, S. Larsson, Variability of the pullout strength of cancellous bone screws with cement augmentation, Clin. Biomech. 30 (2015) 500–506.
[216] D.-H. Lee, S.-H. Lee, E.-K. Song, J.-K. Seon, H.-A. Lim, H.-Y. Yang, Causes and clinical outcomes of revision total knee arthroplasty, Knee surgery & related research 29 (2017) 104.
[217] E. Greenfield, "Inventor, Mounting of artificial teeth," *US Patent Office*, vol. 478360, 1909.
[218] R.J. Rudy, P.A. Levi Jr., F.J. Bonacci, A.S. Weisgold, D. Engler-Hamm, Intraosseous anchorage of dental prostheses: an early 20th century contribution, Compendium 29 (2008) 220.
[219] J. Galante, W. Rostoker, Fiber metal composites in the fixation of skeletal prosthesis, J. Biomed. Mater. Res. A 7 (1973) 43–61.
[220] A. Nouri, P.D. Hodgson, C.e. Wen, Biomimetic porous titanium scaffolds for orthopedic and dental applications, Biomimetics Learning from Nature, InTech, 2010.
[221] F. Matassi, A. Botti, L. Sirleo, C. Carulli, M. Innocenti, Porous metal for orthopedics implants, Clinical cases in mineral and bone metabolism 10 (2013) 111.
[222] P. Lichte, H. Pape, T. Pufe, P. Kobbe, H. Fischer, Scaffolds for bone healing: concepts, materials and evidence, Injury 42 (2011) 569–573.
[223] G. McKee, J. Watson-Farrar, Replacement of arthritic hips by the McKee-Farrar prosthesis, Bone & joint journal 48 (1966) 245–259.
[224] G. Bellefontaine, University of Birmingham (Ed.), The Corrosion of CoCrMo Alloys for Biomedical Applications, 2010.
[225] T.W. Bauer, J. Schils, The pathology of total joint arthroplasty, Skelet. Radiol. 28 (1999) 423–432.
[226] M.B. Nasab, M.R. Hassan, B.B. Sahari, Metallic biomaterials of knee and hip-a review, Trends Biomater. Artif. Organs 24 (2010) 69–82.
[227] J.R.P. Jorge, V.A. Barao, J.A. Delben, L.P. Faverani, T.P. Queiroz, W.G. Assunçao, Titanium in dentistry: historical development, state of the art and future perspectives, The journal of indian prosthodontic society 13 (2013) 71–77.
[228] R. Saha, K. Jacob, Casting of titanium and its alloys, Def. Sci. J. 36 (2014) 121–141.
[229] F. Witte, H. Ulrich, C. Palm, E. Willbold, Biodegradable magnesium scaffolds: part II: peri-implant bone remodeling, J. Biomed. Mater. Res. A 81 (2007) 757–765.
[230] C. Janning, E. Willbold, C. Vogt, J. Nellesen, A. Meyer-Lindenberg, H. Windhagen, et al., Magnesium hydroxide temporarily enhancing osteoblast activity and decreasing the osteoclast number in peri-implant bone remodelling, Acta Biomater. 6 (2010) 1861–1868.
[231] K. Mediaswanti, C. Wen, E. Ivanova, C. Berndt, F. Malherbe, V. Pham, et al., A review on bioactive porous metallic biomaterials, Journal of biomimetics biomaterials and tissue engineering 18 (2013) 1–8.
[232] B.R. Levine, S. Sporer, R.A. Poggie, C.J. Della Valle, J.J. Jacobs, Experimental and clinical performance of porous tantalum in orthopedic surgery, Biomaterials 27 (2006) 4671–4681.
[233] M.P. Staiger, A.M. Pietak, J. Huadmai, G. Dias, Magnesium and its alloys as orthopedic biomaterials: a review, Biomaterials 27 (2006) 1728–1734.
[234] L.D. Zardiackas, D.E. Parsell, L.D. Dillon, D.W. Mitchell, L.A. Nunnery, R. Poggie, Structure, metallurgy, and mechanical properties of a porous tantalum foam, J. Biomed. Mater. Res. A 58 (2001) 180–187.
[235] N. Patil, K. Lee, S.B. Goodman, Porous tantalum in hip and knee reconstructive surgery, J. Biomed. Mater. Res. B Appl. Biomater. 89 (2009) 242–251.
[236] P.J. Brooks, P.S. Walker, R.D. Scott, Tibial component fixation in deficient tibial bone stock, Clin. Orthop. Relat. Res. (184) (1984) 302-308.
[237] B. Levine, S. Sporer, C.J. Della Valle, J.J. Jacobs, W. Paprosky, Porous tantalum in reconstructive surgery of the knee–a review, Journal of Knee Surgery 20 (2007) 185–194.
[238] R.M. Meneghini, D.G. Lewallen, A.D. Hanssen, Use of porous tantalum metaphyseal cones for severe tibial bone loss during revision total knee replacement, J bone & joint surgery (2009) 131–138.
[239] W.J. Long, G.R. Scuderi, Porous tantalum cones for large metaphyseal tibial defects in revision total knee arthroplasty: a minimum 2-year follow-up, J. Arthroplast. 24 (2009) 1086–1092.
[240] A. Gkavardina, P. Tsagozis, The use of megaprostheses for reconstruction of large skeletal defects in the extremities: a critical review, The open orthopaedics journal 8 (2014) 384.

[241] D. Huten, Femorotibial bone loss during revision total knee arthroplasty, Orthopaedics & Traumatology: Surgery & Research 99 (2013) S22–S33.
[242] A.F. Kamal, P. Rubiansyah, Clinical outcome of various limb salvage surgeries in osteosarcoma around knee: Megaprosthesis, extracorporeal irradiation and re-section arthrodesis, Annals of Medicine and Surgery 42 (2019) 14–18.
[243] S. Höll, A. Schlomberg, G. Gosheger, R. Dieckmann, A. Streitbuerger, D. Schulz, et al., Distal femur and proximal tibia replacement with megaprosthesis in revision knee arthroplasty: a limb-saving procedure, Knee Surg. Sports Traumatol. Arthrosc. 20 (2012) 2513–2518.
[244] B.D. Springer, F.H. Sim, A.D. Hanssen, D.G. Lewallen, The modular segmental kinematic rotating hinge for nonneoplastic limb salvage, Clin. Orthop. Relat. Res. 421 (2004) 181–187.
[245] D. Back, L. David, A. Hilton, G. Blunn, T. Briggs, S. Cannon, The SMILES prosthesis in salvage revision knee surgery, Knee 15 (2008) 40–44.
[246] K.R. Berend, A.V. Lombardi, Distal femoral replacement in nontumor cases with severe bone loss and instability, Clin. Orthop. Relat. Res. 467 (2009) 485–492.
[247] K. Vertesich, S.E. Puchner, K. Staats, M. Schreiner, C. Hipfl, B. Kubista, et al., Distal femoral reconstruction following failed total knee arthroplasty is accompanied with risk for complication and reduced joint function, BMC Musculoskelet. Disord. 20 (2019) 47.
[248] S.D. Stulberg, Bone loss in revision total knee arthroplasty: graft options and adjuncts, J. Arthroplast. 18 (2003) 48–50.
[249] M.G. Brand, R.J. Daley, F.C. Ewald, R.D. Scott, Tibial tray augmentation with modular metal wedges for tibial bone stock deficiency, Clin. Orthop. Relat. Res. 248 (1989) 71–79.
[250] P. Sculco, M. Abdel, A.D. Hanssen, D. Lewallen, The management of bone loss in revision total knee arthroplasty: rebuild, reinforce, and augment, Bone joint j 98 (2016) 120–124.
[251] M. Vasso, P. Beaufils, S. Cerciello, A.S. Panni, Bone loss following knee arthroplasty: potential treatment options, Arch. Orthop. Trauma Surg. 134 (2014) 543–553.
[252] M. Fosco, R.B. Ayad, L. Amendola, D. Dallari, D. Tigani, Management of bone loss in primary and revision knee replacement surgery, Recent Advances in Arthroplasty, InTech, 2012.
[253] D. Kendoff, R. Morgan-Jones, F.S. Haddad, Periprosthetic Joint Infections: Changing Paradigms, (2016).
[254] C.L. Jensen, M.M. Petersen, H.M. Schrøder, B. Lund, Bone mineral density changes of the proximal tibia after revision total knee arthroplasty. A randomised study with the use of porous tantalum metaphyseal cones, Int. Orthop. 36 (2012) 1857–1863.
[255] T. Albrektsson, C. Johansson, Osteoinduction, osteoconduction and osseointegration, Eur. Spine J. 10 (2001) 96–101.
[256] J. Hong, A. Azens, K.N. Ekdahl, C.G. Granqvist, B. Nilsson, Material-specific thrombin generation following contact between metal surfaces and whole blood, Biomaterials 26 (2005) 1397–1403.
[257] T.M. Zimmer, Tibial and Femoral Cones Surgical Techniques, Copyright (2011).
[258] M.F. Meijer, A.L. Boerboom, M. Stevens, I.H.F. Reininga, D.W. Janssen, N. Verdonschot, et al., Tibial component with and without stem extension in a trabecular metal cone construct, Knee surgery, sports, traumatol, arthroscopy 25 (2016) 3644–3652.
[259] D.Y. Ponzio, M.S. Austin, Metaphyseal bone loss in revision knee arthroplasty, Current reviews in musculoskeletal medicine 8 (2015) 361–367.
[260] F. Chen, K.A. Krackow, Management of tibial defects in total knee arthroplasty. A biomechanical study, Clin. Orthop. Relat. Res. 305 (1994) 249–257.
[261] D.M. Findlay, K. Welldon, G.J. Atkins, D.W. Howie, A.C. Zannettino, D. Bobyn, The proliferation and phenotypic expression of human osteoblasts on tantalum metal, Biomaterials 25 (2004) 2215–2227.
[262] T.W. Huff, T.P. Sculco, Management of bone loss in revision total knee arthroplasty, J. Arthroplast. 22 (2007) 32–36.
[263] T.A. Schildhauer, B. Robie, G. Muhr, M. Köller, Bacterial adherence to tantalum versus commonly used orthopedic metallic implant materials, J. Orthop. Trauma 20 (2006) 476–484.
[264] A.F. Kamath, D.G. Lewallen, A.D. Hanssen, Porous tantalum metaphyseal cones for severe tibial bone loss in revision knee arthroplasty: a five to nine-year follow-up, JBJS 97 (2015) 216–223.
[265] P.F. Lachiewicz, M.P. Bolognesi, R.A. Henderson, E.S. Soileau, T.P. Vail, Can tantalum cones provide fixation in complex revision knee arthroplasty? Clin. Orthop. Relat. Res. 470 (2012) 199–204.
[266] G.D. Potter III, M.P. Abdel, D.G. Lewallen, A.D. Hanssen, Midterm results of porous tantalum femoral cones in revision total knee arthroplasty, JBJS 98 (2016) 1286–1291.
[267] G. Burastero, L. Cavagnaro, F. Chiarlone, M. Alessio-Mazzola, G. Carrega, L. Felli, The use of tantalum metaphyseal cones for the management of severe bone defects in septic knee revision, J. Arthroplast. 33 (2018) 3739–3745.
[268] A. Zanirato, L. Cavagnaro, M. Basso, S. Divano, Metaphyseal sleeves in total knee arthroplasty revision: complications, clinical and radiological results. A systematic review of the literature, Arch. Orthop. Trauma Surg. 138 (2018) 993–1001, https://doi.org/10.1007/s00402-018-2967-0.
[269] C. Jiang, W. Qian, Results of sleeves in revision total knee arthroplasty: an editorial comment on recently published in the journal of arthroplasty, Annals of translational medicine 3 (2015).
[270] D.F. Dalury, W.P. Barrett, The use of metaphyseal sleeves in revision total knee arthroplasty, Knee 23 (2016) 545–548.
[271] S. Agarwal, A. Azam, R. Morgan-Jones, Metal metaphyseal sleeves in revision total knee replacement, Bone joint j 95 (2013) 1640–1644.
[272] K.E. Bugler, R. Maheshwari, I. Ahmed, I.J. Brenkel, P.J. Walmsley, Metaphyseal sleeves for revision total knee arthroplasty: good short-term outcomes, J. Arthroplast. 30 (2015) 1990–1994.
[273] P. Christen, K. Ito, R. Ellouz, S. Boutroy, E. Sornay-Rendu, R.D. Chapurlat, et al., Bone remodelling in humans is load-driven but not lazy, Nat. Commun. 5 (2014) 4855.
[274] P.A. Downey, M.I. Siegel, Bone biology and the clinical implications for osteoporosis, Phys. Ther. 86 (2006) 77–91.
[275] M.P. Quilez, B. Seral, M.A. Pérez, Biomechanical evaluation of tibial bone adaptation after revision total knee arthroplasty: a comparison of different implant systems, PLoS One 12 (2017) e0184361.
[276] G.E. Alexander, T.L. Bernasek, R.L. Crank, G.J. Haidukewych, Cementless metaphyseal sleeves used for large tibial defects in revision total knee arthroplasty, J. Arthroplast. 28 (2013) 604–607.
[277] S.L. Barnett, R.R. Mayer, J.S. Gondusky, L. Choi, J.J. Patel, R.S. Gorab, Use of stepped porous titanium metaphyseal sleeves for tibial defects in revision total knee arthroplasty: short term results, J. Arthroplast. 29 (2014) 1219–1224.
[278] R. Huang, G. Barrazueta, A. Ong, F. Orozco, M. Jafari, C. Coyle, et al., Revision total knee arthroplasty using metaphyseal sleeves at short-term follow-up, Orthopedics 37 (2014) e804–e809.
[279] M. Thorsell, M. Hedström, M.C. Wick, R.J. Weiss, Good clinical and radiographic outcome of cementless metal metaphyseal sleeves in total knee arthroplasty: retrospective study of 31patients with minimum 5-year follow-up, Acta Orthop. 89 (2018) 84–88.
[280] N. Wirries, H.J. Winnecken, G. von Lewinski, H. Windhagen, M. Skutek, Osteointegrative sleeves for metaphyseal defect augmentation in revision total knee arthroplasty: clinical and radiological 5-year follow-up, J. Arthroplast. (2019), https://doi.org/10.1016/j.arth.2019.04.024.
[281] K.L. Scott, M.P. Abdel, A.D. Hanssen, Metaphyseal sleeves and cones in revision total knee arthroplasty, Revision Total Knee Arthroplasty, Springer, 2018, pp. 131–141.
[282] J. Nadorf, S. Kinkel, S. Gantz, E. Jakubowitz, J.P. Kretzer, Tibial revision knee arthroplasty with metaphyseal sleeves: the effect of stems on implant fixation and bone flexibility, PLoS One 12 (2017) e0177285.
[283] G. Stefani, V. Mattiuzzo, G. Prestini, Revision total knee arthroplasty with metaphyseal sleeves without stem: short-term results, Joints 5 (2017) 207–211.
[284] A. Faizan, M. Bhowmik-Stoker, V. Alipit, A.E. Kirk, V.E. Krebs, S.F. Harwin, et al., Development and verification of novel porous titanium metaphyseal cones for revision total knee arthroplasty, J. Arthroplast. 32 (2017) 1946–1953.
[285] K. Denehy, S. Abhari, V.E. Krebs, C.A. Higuera-Rueda, L.T. Samuel, A.A. Sultan, et al., Excellent metaphyseal fixation using highly porous cones in revision total knee arthroplasty, J. Arthroplast. (2019), https://doi.org/10.1016/j.arth.2019.03.045.
[286] T. Mäkinen, M. Abolghasemian, E. Watts, S. Fichman, P. Kuzyk, O. Safir, et al., Management of massive acetabular bone defects in revision arthroplasty of the hip using a reconstruction cage and porous metal augment, The bone & joint journal 99 (2017) 607–613.
[287] G.J. Haidukewych, A. Hanssen, Metaphyseal fixation in revision total knee arthroplasty: indications and techniques, JAAOS 19 (2011) 311–318.
[288] G. Ceccarelli, R. Presta, L. Benedetti, M.G. Cusella De Angelis, S.M. Lupi, R. Rodriguez y Baena, Emerging perspectives in scaffold for tissue engineering in oral surgery, Stem Cells Int. 2017 (2017) 4585401, , https://doi.org/10.1155/2017/4585401 (11 pages).
[289] W. Schlickewei, C. Schlickewei, The use of bone substitutes in the treatment of bone defects–the clinical view and history, Macromolecular Symposia, 2007, pp. 10–23.