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SUPPLEMENT ARTICLE

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# Bone grafts: which is the ideal biomaterial?

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## Abstract

Bovine xenograft materials, followed by synthetic biomaterials, which unfortunately still lack documented predictability and clinical performance, dominate the market for the cranio-maxillofacial area. In Europe, new stringent regulations are expected to further limit the allograft market in the future.

**Aim:** Within this narrative review, we discuss possible future biomaterials for bone replacement.

**Scientific Rationale for Study:** Although the bone graft (BG) literature is overflooded, only a handful of new BG substitutes are clinically available. Laboratory studies tend to focus on advanced production methods and novel biomaterial features, which can be costly to produce.

**Practical Implications:** In this review, we ask why such a limited number of BGs are clinically available when compared to extensive laboratory studies. We also discuss what features are needed for an ideal BG.

**Results:** We have identified the key properties of current bone substitutes and have provided important information to guide clinical decision-making and generate new perspectives on bone substitutes. Our results indicated that different mechanical and biological properties are needed despite each having a broad spectrum of variations.

**Conclusions:** We foresee bone replacement composite materials with higher levels of bioactivity, providing an appropriate balance between bioabsorption and volume maintenance for achieving ideal bone remodelling.

KEYWORDS

bone graft, bone graft substitute, Bone replacement grafts, deal biomaterial

## 1 | INTRODUCTION

Bone defects resulting from trauma, disease, surgery or congenital malformations are a significant health problem worldwide. Bone is, indeed, the second most transplanted tissue after blood. Several countries are currently experiencing an exceedingly high demand for bone grafts (BGs) and bone tissue engineering solutions. In the United States and Europe, more than half a million patients annually receive bone defect repairs with a cost estimated to be greater than US$3 billion (Amini, Laurencin, & Nukavarapu, 2012; MarketReport, 2017). This number is expected to double globally by 2020 due to a variety of factors, such as the growing needs of the world population, increased life expectancy (Baroli, 2009) and increased access to advanced health services and assistance, particularly in growing countries. The European market for dental BGs has shown improvements in growth due to several factors and trends. A major contributor of this growth has been the healthy expansion of the European dental implant market, particularly in regions where implant penetration has been relatively low (*e.g.* France and the United Kingdom) and in those where it

  

kept growing significantly (*e.g.* Italy and Germany, MarketReport, 2015).

The current gold standard for bone defect repair is still autologous (*i.e.* sourcing the bone from the patients themselves) (Giannoudis, Chris Arts, Schmidmaier, & Larsson, 2011; De Grado et al., 2018). These grafts are, self-evidently, histocompatible and non-immunogenic and offer all of the imperative properties required for a BG. Specifically, autografts possess the essential components to achieve osteoinduction, osteogenesis and osteoconduction (Amini et al., 2012). However, autografts require a secondary surgical procedure at the site of the tissue harvest, which can lead to complications such as donor site injury, morbidity, deformity and scarring. In addition, harvesting and implanting autografts is an expensive procedure that is also associated with high surgical risks, such as bleeding, inflammation, infection, chronic pain and higher costs. Furthermore, autografts may not be a treatment option when the defect site requires large amounts of bone (Ebraheim, Elgafy, & Xu, 2001; St John et al., 2003). In the cranio-maxillofacial area, autografts play a marginal role, being widely overtaken by allografts in the United States and by bovine xenografts in Europe for reasons related to costs/benefits (Jo, S.H. et al., 2018).

Although BGs have been used for decades to improve bone repairs, none of the currently available BGs possess all the desirable characteristics that such a biomaterial should have: high osteoinductive and angiogenic potentials, biological safety, low patient morbidity, high volumetric stability, easy market availability, long shelf life and reasonable production costs (Bose, Roy, & Bandyopadhyay, 2012; Hutmacher, 2006; El-Rashidy, Roether, Harhaus, Kneser, & Boccaccini, 2017). The problems associated with transplanted grafts have raised interest in synthetically improved BGs (Board, 2018; Rothermundt et al., 2014). This can be seen also by the increasing number of publications on BGs. Thompson's Web of Science® shows an almost triplicate in the number of publications using the search terms "bone graft substitute", "bone scaffold" and "bone graft" for the period of 1997–2017 (Figure 1), with more than 6,000 papers published in this field in 2017 alone. The mismatch between the extraordinarily high number of laboratory studies on new BGs and the low number of clinical studies is apparent. From the myriad of solutions suggested by an abundant literature (Figure 1), new BGs that are certified as medical devices and hence made available for the cranio-maxillofacial market are limited. One reason for this gap is the cost margin for BGs in cranio-maxillofacial applications, which limit the market to BGs with complex and costly production processes. Another reason is the relatively low number of clinical studies comparing BGs; some in vivo studies compare different BGs (Araujo, Linder, & Lindhe, 2009; Santos et al., 2010; Benic et al., 2017; Jung et al., 2017; Lambert et al., 2017). Consequently, only a few BGs today dominate the cranio-maxillofacial market. Nonetheless, there is an increasing demand for a new generation of synthetic BGs with a higher degree of bioactivity and mechanical strength and manufactured with cost-efficient methods.

## 2 | REVIEW OF CURRENT LITERATURE

### 2.1 | Literature search

This narrative review follows the guidelines in PRISMA's statement (http://www.prisma-statement.org/). We performed our search on MEDLINE (through the PubMed interface), Google Scholar and Web of Science. We created an ad hoc search string combining keywords with the use of Boolean operators "AND" and "OR". The search string was as follows: (["bone graft material" OR "bone graft substitute"] AND ["bone scaffold" OR "bone formation" OR "regeneration" OR "ideal"). Limits were set to the English language and the year of publication 2000–2018. Additionally, we searched records for "commercial drivers" AND "market limitation" AND "bone graft substitute" AND/OR "bone scaffolds". Although the focus area for this review is the cranio-maxillofacial field, studies from the orthopaedic field have been included to provide more evidence between BG and its interaction with the bone. Regarding the data collection, two reviewers (HJH, GP) independently screened the titles and the abstracts of the initially retrieved articles and other records. Abstracts and records that were not available or did not provide sufficient information were excluded. HJH and GP resolved all disagreements through discussion. To verify inclusion criteria independently, the two reviewers assessed the full texts of all studies of possible relevance. Exclusion criteria were as follows: studies presenting incomplete data (*e.g.* mean values without standard deviations) and quantitative analyses with less than eight total specimens. The researchers recorded their reasons for exclusion at this stage. See the flow chart to examine the record-selection process (Figure 2).

### 2.2 | Properties of an ideal bone graft substitute material

BGs are used to repair and rebuild diseased bones in a human body that is unable to heal the bone by itself. To perform this kind of repair, a porous structure that is capable of supporting new and healthy three-dimensional tissue formation is essential (Huiskes, Ruimerman, van Lenthe, & Janssen, 2000). Attempts to define the ideal BG has already been attempted 30 years ago (Lemons et al., 1988). Despite extensive research in the past 30 years (Figure 1), a BG that meets all these requirements has yet to be developed; yet, we still continue to redefine the BG's desirable properties. A BG should meet specific requirements to achieve its goal. First, an interconnected porosity with an adequate pore size should allow for diffusion throughout the whole BG for bone cells, nutrients and exchange of waste products. The very minimum pore size is around 100 μm; however, pore sizes >300 μm are recommended for allowing vascularization and new bone formation (Karageorgiou & Kaplan, 2005; Murphy, Haugh, & O'Brien, 2010; Saito et al., 2012). The second requirement is a surface that allows vascular ingrowth, bone cell attachment, migration and proliferation. The third is adequate mechanical compressive strength and elasticity for allowing absorbance

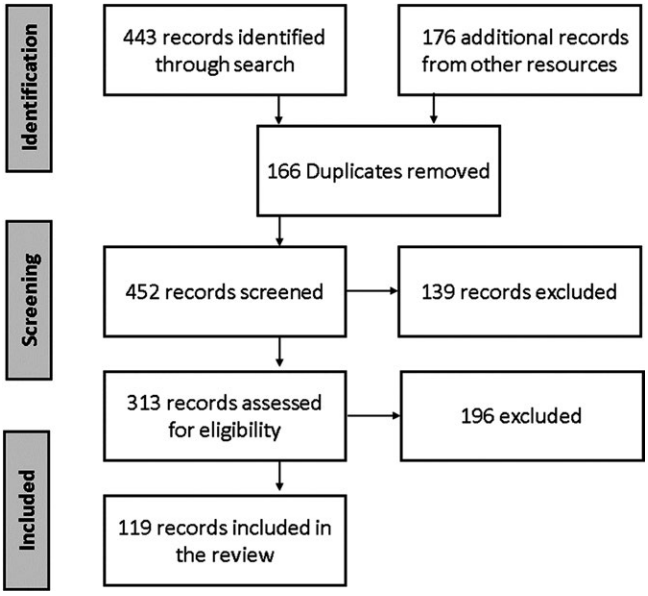


**FIGURE 1** Graphical presentation of number of publications found on Web of Science® after using the search terms "bone graft substitute", "bone scaffold" and "bone graft" for the period of 2007–2017

of the load from surrounding hard and soft tissues in non-contained defects. The fourth is controlled biodegradability, which ensures resorption during the tissue-remodelling process while maintaining defect volume for bone ingrowth. The last requirement is sufficient dimensional stability for allowing the chairside adaptation of the BG to the defect.

The BG can be divided according to several categorizations (Planell, Best, Lacroix, & Merolli, 2009); here, we chose to divide between biological and synthetic biomaterials. The main advantages and disadvantages are listed in Table 1. Independently of the BGs' chemical compositions, other parameters, such as surface morphology and internal pore architecture like pore size, porosity, interconnectivity and pore structure, control for their osteoconductive properties (Kasten et al., 2008; von Doernberg et al., 2006). Another important condition is the resorbability of the materials. An ideal BG substitute is expected to be replaced by bone and remodelled at a tailored absorption rate (Williams, 2008; Murphy et al., 2010). Ideally, cells such as osteoclasts and macrophages should resorb or dissolve synthetic BG substitutes (Schmidt-Rohlfing, Tzioupis, Menzel, & Pape, 2009), while materials like polymers are degraded mainly hydrolytically or enzymatically. The chemical stability of synthetic biomaterials often impedes these mechanisms (Planell et al., 2009; Corbella, Taschieri, Weinstein, & Del Fabbro, 2016; Ceccarelli et al., 2017).

## 2.3 | Allografts

Allografts, which can include tissue from both living human donors and cadavers, represent the second most common bone-grafting technique worldwide (Amini et al., 2012). An allogenic BG refers to bony tissue that is harvested from one individual and transplanted to a genetically different individual of the same species (Roberts & Rosenbaum, 2012; Goldberg & Akhavan, 2005). Allografts are also similarly histocompatible and available in various forms, including demineralized bone matrices, cancellous chips, cortico-cancellous and cortical grafts and osteochondral and whole-bone segments, depending on the host site's requirements (Finkemeier, 2002a). In comparison with autografts, allografts are associated with risks of immunoreactions and transmission of infections and have numerous proven records of high failure rates over long-term use (De Grado et al., 2018; Winkler, Sass, Duda, & Schmidt-Bleek, 2018). Allografts are devitalized (and often sterilized) mainly through decalcification, deproteinization, irradiation and/or freeze-drying processing; they therefore lack cells and have reduced osteoinductive properties (Wheeler & Enneking, 2005; Delloye, Cornu, Druez, & Barbier, 2007). Finally, as well as importantly, there is an increasing shortage of supplies in tissue donations each year. For all these reasons and due to increased regulatory restrictions particularly in Europe (European Tissue and Cells Directive; EUTCD, 2004) and the new medical device regulation (MDR, 2017), allografts are frequently abandoned in clinical practice. These factors are significant market restraints for manufacturers and hinder the rapid shift from allografts to other BG substitutes (MarketReport, 2017).

## 2.4 | Xenografts

Xenografts involve the transplantation of bone tissue across species. The use of xenotransplantation presents a number of biological challenges, which include the risk of disease transmission (*e.g.* prions and retroviruses), an immune response of the host tissue after implantation (Schroeder & Mosheiff, 2011), lack of viable cells and reduced osteoinductive properties due to manufacturing processes (Zimmermann & Moghaddam, 2011). Bovine xenografts play a major role and have been proven for cranio-maxillofacial applications (Yamada & Egusa, 2018) with no reports on Transmissible Spongiform Encephalopathies (TSE) and Bovine Spongiform Encephalopathy (BSE) risk (Kim, Nowzari, & Rich, 2013). Results from a large retrospective analysis with long-term observation time (Knofler, Barth, Graul, & Krampe, 2016), together with a systematic review of survival data, indicate that synthetic graft materials are associated with lower dental implant survival rates than bovine cancellous bone substitutes (Aghaloo & Moy, 2007). Nevertheless, in randomized control clinical trials (Mardas, Chadha, & Donos, 2010; Mardas, D'Aiuto, Mezzomo, Arzoumanidi, & Donos, 2011) with a synthetic bone substitute or bovine xenograft, both types of BGs presented similar radiographic alveolar bone changes when used for alveolar ridge preservation. The same results were also obtained when a BG was placed adjacent to a dental implant (Patel, Mardas, & Donos, 2013). Systematic reviews have reported a reduction in superiorly weighted mean defects when used for lateral bone augmentation around dental implants, although no randomized controlled trials (RCT) to date have compared different bone replacement grafts, and the number of reported cases that reacted to xenografts is significantly higher

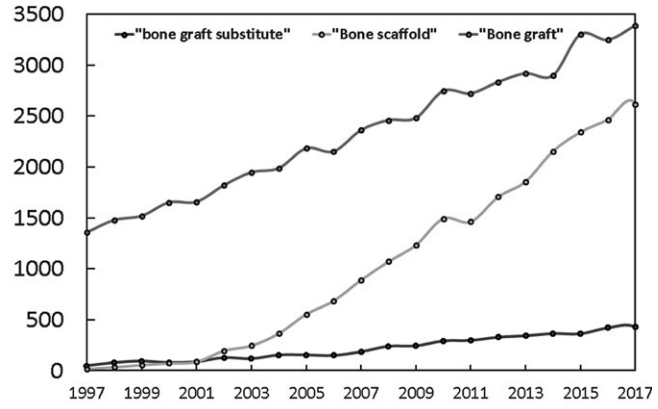


**FIGURE 2** Flowchart of the record-selection process

than the rest of the biomaterials (Sanz-Sanchez, Ortiz-Vigon, Sanz-Martin, Figuero, & Sanz, 2015).

## 2.5 | Natural biomaterials

The use of natural polymers for bone replacement can be elucidated due to their similarity to the native extracellular matrix (ECM) and according to their chemical composition. These polymers can be divided into three classes as follows: (a) proteins (collagen, gelatine, fibrinogen, elastin); (b) polysaccharides (glycosaminoglycans, cellulose, amylose); and (c) polynucleotides (DNA, RNA) (Corbella et al., 2016; Ceccarelli et al., 2017; Ghassemi et al., 2018). Their resemblance to native ECMs results in high osteoinductive properties. Several strategies have been proposed for fabricating a natural polymeric BG: they can be derived by cells, which are inducted to produce an ECM, or directly obtained from decellularized bone tissue (Pei, Li, Shoukry, & Zhang, 2011). Autologous ECM-based bone substitutes are highly biocompatible and display very little risk of host immune reactions; however, the need for an additional surgery to sample grafts, with consequent loco-regional morbidity and limited availability of tissue, has not been a negligible limitation to this approach, similarly to autologous substitutes. Allografts and xenografts, in contrast, show no concerns about biomaterial availability and have high osteoinductive and osteoblast stimulation properties; however, possible host immune reactions and risk of disease transmission are still concerns, particularly for allograft-derived ECM-based grafts. Natural BG polymers have been demonstrated to provide mesenchymal stem cell differentiation to the osteoblast (Wang, Kim, Blasioli, Kim, & Kaplan, 2005; Chung & Burdick, 2008). However, mechanical properties are quite poor and biodegradability is less controllable in naturally derived biomaterials compared to synthetic polymers (Mano et al., 2007; Hannink & Arts, 2011).

## 2.6 | Synthetic materials

### 2.6.1 | Synthetic polymers

Synthetic polymers have demonstrated the promising potential to be biomaterials for bone tissue engineering due to their controllable and tuneable biomechanical and biodegradability properties. Moreover, they provide better controllability in terms of porosity, physiochemical structure and immunologic adverse effects when compared to other types of BG substitutes (Fuchs, Nasseri, & Vacanti, 2001; Kretlow & Mikos, 2007). The most studied synthetic polymers in bone tissue regeneration are aliphatic polyesters like poly(lactic acid) (PLA), poly(ε-caprolactone) and poly(glycolic acid), as well as their copolymers and derivatives. These polymers are degraded by hydrolysis in vivo and have the advantage of being easily tailored in different shapes, according to the mechanical demands in the particular bone treated (Yan et al., 2011; Ali Akbari Ghavimi, Ebrahimzadeh, Solati-Hashjin, & Abu Osman, 2015; Pilipchuk et al., 2015). However, synthetic polymers still show some concerns about osteoconductivity, absorption timing and local pH alterations. Additionally, all polymers' surfaces have the disadvantage of proving inferior cell attachment properties. Other synthetic polymers include poly(methyl methacrylate), poly hydroxyl butyrate, polyethylene, polypropylene and polyurethane. Some polymers, such as poly(propylene fumarate), have demonstrated great resistance to compressive stress and a controlled biodegradability; however, their degradation has led to the release of acid compounds that could constitute an adverse issue on the native bone (Hedberg et al., 2005).

### 2.6.2 | Synthetic bioceramics

Synthetic bioceramics can be classified into several groups according to their silicate content (Figure 3) (Müller, 2015; Bengisu, 2016) because silicate seems to play a vital role in bone tissue engineering (Oliveira, Malafaya, & Reis, 2003; Gaharwar et al., 2013; Xavier et al., 2015). Calcium sulphate, calcium phosphate (CaP) ceramics, bioactive glass and combinations thereof are the most common synthetic bone substitutes available at present (Yang, Lin, Zhang, & Gou, 2013). They are of special interest as these BGs have compositional similarities to natural bone (Finkemeier, 2002b).

CaP has received little or no attention for bone-related applications because of its biocompatibility, biodegradability and similarity in structure to the inorganic composition of bone minerals (Bose & Tarafder, 2012). When compared to metals and polymers, synthetic bioceramics are superior for bone repairs due to their improved biocompatibility, bioactivity and strength (Baino, Novajra, & Vitale-Brovarone, 2015; Hing, 2005). The use of CaP is motivated by the fact that the primary inorganic component of bone is calcium hydroxyapatite, a subset of the CaP group (Elliott, 2002). In contrast, mechanical properties are major disadvantages of synthetic bioceramics and limit their use in load-bearing applications (Huang, Wang, & Wang, 2014; Park, 2008). Improvement of the manufacturing processes, which eliminate structural flaws (Tiainen, Wiedmer, & Haugen, 2013) or improve microstructural features (Georgiou & Knowles, 2001; De Aza, Chevalier, Fantozzi, Schehl, & Torrecillas, 2002) or composite structures (Miao, Tan, Li, Xiao, & Crawford, 2008; Novak, Druce, Chen, & Boccaccini, 2009), is alternatives in improving the intrinsic strength of synthetic bioceramics. The most investigated CaP BG substitutes are hydroxyapatite, beta-tricalcium phosphate and their

**TABLE 1** Summary of main advantages and disadvantages of BG

| Bone graft (BG) | Advantages | Disadvantages |
|---|---|---|
| Autologous | • high osteoconductivity<br>• highest degree of biological safety<br>• no risk of immune reaction | Need of an additional surgery |
| Xenografts | • architecture and geometric structure resemble bone<br>• Well documented<br>• predictable clinical outcome<br>• slow bio-absorbability preserves augmented bone volume | • possible disease transmission and potential unwanted immune reactions<br>• lacks viable cells and biological components<br>• resorption rate is highly variable<br>• reduced future availability due European regulatory changes ? |
| Natural biomaterials | Similarity to native extracellular matrix | Mechanical properties poor<br>-biodegradability less controllable |
| Synthetic polymers | • tuneable physicochemical properties<br>• tuneable degradability | • low cell attachment<br>• timing of absorption (alteration of mechanical properties)<br>• release of acidic degradation products |
| Synthetic bioceramics | • high biocompatibility<br>• osteoinductive properties<br>• chemical similarity with bone<br>• stimulation of osteoblast growth | • high brittleness<br>• low ductility<br>• not predictable absorption |
| Composite xenohybrid substitutes | • high similarity with human cancellous bone<br>• higher bioactivity<br>• tailored degradation rates<br>• incorporation of active biomolecules | • cleaning and sterilization process partially alters biological performances<br>• limited clinical data |

combination, also called biphasic calcium phosphate (Dorati et al., 2017). Synthetic bioceramics have demonstrated the ability to partially integrate into natural bone tissue and stimulate osteoblast differentiation, osteoblast growth and inorganic matrix deposition. In addition to CaP's composition, structure and crystallinity also play a role in how osteoblasts proliferate and differentiate when in contact with CaP and can be partially tuned as needed during the fabrication process (Laurencin, Khan, & Veronick, 2014). However, the clinical applications of CaP bone substitutes are limited by their fragility, as well as their unpredictable absorption rate while not being able to maintain their defect volume, which makes the CaP have overall less favourable clinical outcomes. Thus, new bone tissue formed in a CaP BG mostly cannot sustain mechanical loading and natural bone, and such biomaterials are mainly used for particulates and applied to bone-void fillings in low-load-bearing applications. More recently, it has been shown that doping CaP BG with various compounds could improve mechanical resistance, biocompatibility and absorption rate. For instance, Fielding, Bandyopadhyay, and Bose (2012) demonstrated that the addiction of silicon and zinc oxides to beta-tricalcium phosphate increased compressive strength to 2.5-fold and cell viability to 92%; however, clinical evidence is still lacking. Bioglass® such as 45S5 experiences the same issue with lower mechanical strength and locally increased in pH values, despite excellent material-bone interactions (Chen, Thompson, & Boccaccini, 2006; Jones, Ehrenfried, & Hench, 2006; Wu, Luo, Cuniberti, Xiao, & Gelinsky, 2011). Other ceramics, like titanium dioxide, have demonstrated biocompatibility and osteoconductive properties in vitro (Verket et al., 2012; Sabetrasekh et al., 2010; Gomez-Florit et al., 2012) and in vivo (Tiainen, Wohlfahrt, Verket, Lyngstadaas, & Haugen, 2012; Haugen et al., 2013). Although in vivo animal model data are promising, clinical data are still lacking. Furthermore, new approaches to the problem of brittleness of ceramic BG substitutes include composite materials in which CaP is mixed with organic polymers (Laurencin et al., 2014). Composite BGs also demonstrated a promising role in drug delivery, thanks to their porosity and cell adhesion ability (Alves Cardoso, Jansen, & Leeuwenburgh, 2012).

### 2.6.3 | Combination of synthetic and xenograft bone graft substitutes (xenohybrid)

It is a generally accepted paradigm that bone substitutes should resemble naturally occurring human cancellous bone as closely as

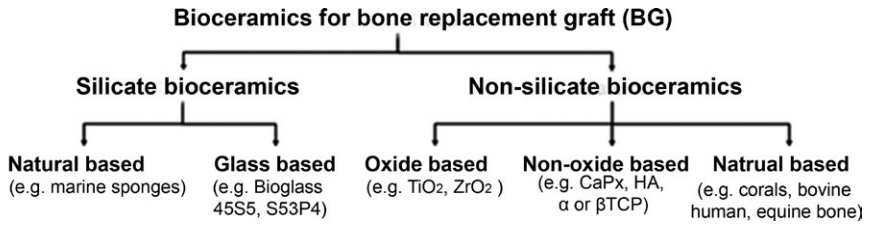


**FIGURE 3** Classification of bioceramic bone grafts divided into silicate and non-silicate ceramics according to their main composition (adapted from Müller 2016)

possible. Therefore, a very commonly used source of bone matrices is animal-derived bones; bovine xenografts, distantly followed by equine and porcine, are commonly used in clinical practice. Bovine-derived cancellous BGs are acknowledged as the closest xenograft to human bone to be regenerated, second only to autografts (Datta, Gheduzzi, & Miles, 2006; Athanasiou et al., 2010), and are considered safe products that can be used daily in clinical practices where bone regeneration is needed in reconstructive surgeries (Capanna et al., 2014; Knofler et al., 2016). However, necessary cleaning and sterilization processes for starting, raw materials of animal origin result in the decay of both mechanical and biological performances (Vishwakarma, Sharpe, Shi, & Ramalingam, 2014). Indeed, similarly to what has been seen for synthetic biomaterials, the application of combining synthetic materials with xenografts is becoming an interesting trend, not only in research (Ceccarelli et al., 2017) but also in industrial and clinical practices (Pertici, Rossi, Casalini, & Perale, 2014; Stacchi et al., 2018). Some studies claim that this combination—this new generation of BG—provides enhanced clinical performance (Pertici et al., 2014; Rossi, Santoro, & Perale, 2015; D'Alessandro et al., 2017; Stacchi et al., 2018), even though clear evidence of osteoinductivity does not yet exist (Roato et al., 2018). Adding resorbable polymeric components can also be used to local, carry active molecules, or drugs to be delivered locally, to increase cell colonization, promote osteoinduction and, finally, promote osteogenesis (D'Alessandro et al., 2017; Roato et al., 2018).

## 3 | DISCUSSION

There is an increasing awareness of allografts and bone substitutes in general, but European dentists still prefer xenografts as substitutes due to their clinical predictability. More scientific literature and comparative studies need to be provided to convince dentists that new BGs can provide more advantages than current xenografts (Larsson & Hannink, 2011). Given that the supply of allografts may be limited in the future, dentists should consider substituting such grafts with more synthetics ones (Bostrom & Seigerman, 2005; Bohner, 2010). Synthetic and composite BGs are progressively being incorporated into cranio-maxillofacial treatments as dentists are becoming aware of their benefits.

In the cranio-maxillofacial area, few competitors lead the market; indeed, the European BG market is dominated by one company, a large manufacturer that holds more than half of all market shares (MarketReport, 2017). Manufacturers are required to assess their products through extensive clinical trials to demonstrate their clinical efficacy and reduce potential risks with respect to gold standards. The results emerging from clinical trials are an important factor that surgeons should use when they select products. For example, a porous beta-tricalcium phosphate has gained positive acceptance since its introduction because of the successful clinical trial outcomes surrounding it (Damron, 2007; Sinha, Menon, & Chakranarayan, 2009; Damron et al., 2013). However, although allografts and Demineralized bone matrix products were used successfully for several years, their high costs and lack of substantial clinical data hindered revenue growth. The recent development of novel BG substitutes is associated with advanced production methods such as 3D printing (Inzana et al., 2014). The mass production of this material can therefore be difficult and costly. Because these materials generate lower revenues in the market, introducing such novel BGs to the market can be challenging. Biomaterial scientists working in the academic field often do not consider scale-up and certification-related problems when developing a new biomaterial for bone tissue engineering purposes.

Synthetic materials have the lowest osteoinductivity of any of the major BG types and are not as widely accepted as the allograft materials (Garcia-Gareta, Coathup, & Blunn, 2015; Miron et al., 2016). Despite the obvious benefits of a synthetic BG, they still lack significant market penetration due to the lack of documented clinical studies supporting their effectiveness. This lack of acceptance has translated into a preference for xenografts over synthetic materials among the majority in the cranio-maxillofacial field. Although this preference hinders synthetic BGs from gaining more market shares, a recent medical device regulation may provide a new market opportunity for synthetic BGs (MarketReport, 2018, MDR, 2017).

As Yamada & Egusa, (2018) concluded in a recent review: "Autogenous bone is still the gold standard and accelerates initial bone formation to a greater extent than bone substitutes. However, autogenous bone is only effective under favourable recipient conditions and thus requires supplementation with bone substitutes in bone augmentation under severe recipient conditions. The biocompatibility of current bone substitute materials should be improved". With respect to this statement, we agree that current bone replacement graft materials need to be "smarter" and elicit a more desirable host response, not only for regular patients but also for more challenging cases. In this field, several drug therapies have been studied for their potential in enhancing bone–tissue healing. Historically, growth factors have attracted considerable attention because they are fundamental for bone regeneration. Bone morphogenetic protein-2 (BMP-2)

and bone morphogenetic protein-7 (BMP-7) are the most extensively investigated growth factors due to their ability to promote differentiation in mesenchymal stem cells to osteoblasts (Chen, Deng, & Li, 2012; Grayson et al., 2015; Scarfi, 2016). However, the administration of recombinant BMPs have been used in concentrations overshooting physiologically occurring concentrations in orthopaedic settings and has raised concerns about documented side effects (Boraiah, Paul, Hawkes, Wickham, & Lorich, 2009; Emara, Diab, & Emara, 2015; Epstein, 2013). The parathyroid hormone, which has already been approved for the treatment of osteoporosis, could also be a valid therapy for bone healing (Vahle et al., 2002; Pilitsis, Lucas, & Rengachary, 2002). Bisphosphonates have been demonstrated as optimal drugs for targeting bones and are among the most studied molecules in the field. Several studies proved their efficacy by carrying antibiotics or chemotherapy agents to the bone and accredited their affinity to hydroxyapatite (Stapleton et al., 2017). Antibodies have also been suggested as a model to target the bone in diverse conditions. In addition, novel approaches including small molecules and peptides (and synthetic derivatives thereof), like steroids, prostaglandin agonists, collagen, amelogenins and Wnt/beta-catenin agonists have been explored, as they are relatively stable, affordable and display little immunogenicity (Lo, Ashe, Kan, & Laurencin, 2012; Hoffman & Benoit, 2015; Benoit, Nuttelman, Collins, & Anseth, 2006). Synthetic derivatives of the aforementioned molecules have shown a positive influence in in vitro and in vivo studies (Rubert et al., 2013; Villa et al., 2015). An alternative strategy is represented by the delivery of nucleotides such as siRNA and miRNA, which can be used to genetically rearrange cells acting at the site of healing and thus improve the regeneration of bone tissue (Murata et al., 2014; Wang, Malcolm, & Benoit, 2017). It should be noted that all these strategies result in products that will be considered as pharmaceutical entities and not medical devices, with additional regulatory consequences and higher costs.

## 4 | CONCLUSIONS

Depending on the clinical problem, different types of substitutes or combinations thereof are necessary. Even though the ideal properties of BG have already been defined in the literature three decades ago, the market still has no available biomaterials that meet all of these properties. The evolution of new-generation BGs continues to evolve with novel biomaterials and processing methods such as additive manufacturing. Current changes in EU regulations of medical devices may increase the use of synthetic materials.

The ideal BG in the future will likely contain a combination of biomaterials with varying features that can control mechanical properties, pore morphology, interconnective pores, surface structure, release of active bone-promoting biomolecules and controlled biodegradability, which ensures resorption during the tissue-remodelling process while maintaining the defect volume for bone ingrowth. These features will improve osteoinduction compared to today's BG material.

Because few comparative studies have reported on in vivo and clinically different BGs, the obvious benefits of newer BGs are not documented well enough. For future BGs to gain market penetration, there is a desire for further comparative studies that use standardized and validated pre-clinical models, both to screen models in small animals but also provide validation to large-animal models.

## CONFLICT OF INTEREST

Lyngstadaas and Haugen hold patents for the technology for the TiO2 bone graft substitute as cited in the reference list (EP Patent 2,121,053, US Patent 9,629,941 US Patent App. 14/427,901, US Patent App. 14/427,683, US Patent App. 14/427,854). The rights for these patents are shared between the University of Oslo and Corticalis AS. Haugen is a shareholder and board member of Corticalis AS. Lyngstadaas is the CEO and a board member of Corticalis AS. Giuseppe Perale is a founding shareholder and the executive vice president of Industrie Biomediche Insubri S.A. (Switzerland), a company that fully owns all IPRs (EP Patent EP2358407B1) on SmartBone® and its technology.

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## REFERENCES

Aghaloo, T. L., & Moy, P. K. (2007). Which hard tissue augmentation techniques are the most successful in furnishing bony support for implant placement? *International Journal of Oral & Maxillofacial Implants*, *22*, 49–70.

Ali Akbari Ghavimi, S., Ebrahimzadeh, M. H., Solati-Hashjin, M., & Abu Osman, N. A. (2015) Polycaprolactone/starch composite: Fabrication, structure, properties, and applications. *Journal of Biomedical Materials Research Part A 103*, 2482–2498. https://doi.org/10.1002/jbm.a.35371

Alves Cardoso, D., Jansen, J. A., & Leeuwenburgh, S. C. (2012). Synthesis and application of nanostructured calcium phosphate ceramics for bone regeneration. *Journal of Biomedical Materials Research. Part B, Applied Biomaterials*, *100B*, 2316–2326. https://doi.org/10.1002/jbm.b.32794

Amini, A. R., Laurencin, C. T., & Nukavarapu, S. P. (2012). Bone tissue engineering: Recent advances and challenges. *Critical Reviews in Biomedical Engineering*, *40*, 363–408. https://doi.org/10.1615/CritRevBiomedEng.v40.i5.10

Araujo, M., Linder, E., & Lindhe, J. (2009). Effect of a xenograft on early bone formation in extraction sockets: An experimental study in dog. *Clinical Oral Implants Research*, *20*, 1–6. https://doi.org/10.1111/j.1600-0501.2008.01606.x

Athanasiou, V. T., Papachristou, D. J., Panagopoulos, A., Saridis, A., Scopa, C. D., & Megas, P. (2010). Histological comparison of autograft,

allograft-DBM, xenograft, and synthetic grafts in a trabecular bone defect: An experimental study in rabbits. *Medical Science Monitor 16*: BR24–BR31.

Baino, F., Novajra, G., & Vitale-Brovarone, C. (2015). Bioceramics and scaffolds: A winning combination for tissue engineering. *Frontiers in Bioengineering and Biotechnology*, *3*, 202. https://doi.org/10.3389/fbioe.2015.00202

Baroli, B. (2009). From natural bone grafts to tissue engineering therapeutics: Brainstorming on pharmaceutical formulative requirements and challenges. *Journal of Pharmaceutical Sciences*, *98*, 1317–1375. https://doi.org/10.1002/jps.21528

Bengisu, M. (2016). Borate glasses for scientific and industrial applications: A review. *Journal of Materials Science*, *51*, 2199–2242. https://doi.org/10.1007/s10853-015-9537-4

Benic, G. I., Thoma, D. S., Jung, R. E., Sanz-Martin, I., Unger, S., Cantalapiedra, A., & Hammerle, C. H. F. (2017). Guided bone regeneration with particulate vs. block xenogenic bone substitutes: A pilot cone beam computed tomographic investigation. *Clinical Oral Implants Research*, *28*, e262–e270. https://doi.org/10.1111/clr.13011

Benoit, D. S., Nuttelman, C. R., Collins, S. D., & Anseth, K. S. (2006). Synthesis and characterization of a fluvastatin-releasing hydrogel delivery system to modulate hMSC differentiation and function for bone regeneration. *Biomaterials*, *27*, 6102–6110. https://doi.org/10.1016/j.biomaterials.2006.06.031

Board, P. A. T. E. (2018) Adult Soft Tissue Sarcoma Treatment (PDQ®). In: *PDQ cancer information summaries*. Rockville, MD: National Cancer Institute (US).

Bohner, M. (2010). Resorbable biomaterials as bone graft substitutes. *Materials Today*, *13*, 24–30. https://doi.org/Doi 10.1016/S1369-7021(10)70014-6

Boraiah, S., Paul, O., Hawkes, D., Wickham, M., & Lorich, D. G. (2009). Complications of recombinant human BMP-2 for treating complex tibial plateau fractures: A preliminary report. *Clinical Orthopaedics and Related Research*, *467*, 3257–3262. https://doi.org/10.1007/s11999-009-1039-8

Bose, S., Roy, M., & Bandyopadhyay, A. (2012). Recent advances in bone tissue engineering scaffolds. *Trends in Biotechnology*, *30*, 546–554. https://doi.org/10.1016/j.tibtech.2012.07.005

Bose, S., & Tarafder, S. (2012). Calcium phosphate ceramic systems in growth factor and drug delivery for bone tissue engineering: A review. *Acta Biomaterialia*, *8*, 1401–1421. https://doi.org/10.1016/j.actbio.2011.11.017

Bostrom, M. P., & Seigerman, D. A. (2005). The clinical use of allografts, demineralized bone matrices, synthetic bone graft substitutes and osteoinductive growth factors: A survey study. *HSS Journal*, *1*, 9–18. https://doi.org/10.1007/s11420-005-0111-5

Capanna, V., Milano, G., Pagano, E., Barba, M., Cicione, C., Salonna, G., … Logroscino, G. (2014). Bone substitutes in orthopaedic surgery: From basic science to clinical practice. *Journal of Material Science Materials in Medicine*, *25*, 2445–2461. https://doi.org/10.1007/s10856-014-5240-2

Ceccarelli, G., Presta, R., Benedetti, L., Cusella De Angelis, M. G., Lupi, S. M., & Rodriguez, Y. B. R. (2017). Emerging perspectives in scaffold for tissue engineering in oral surgery. *Stem Cells International*, *2017*, 4585401. https://doi.org/10.1155/2017/4585401

Chen, G., Deng, C., & Li, Y. P. (2012). TGF-beta and BMP signaling in osteoblast differentiation and bone formation. *International Journal of Biological Sciences*, *8*, 272–288. https://doi.org/10.7150/ijbs.2929

Chen, Q. Z., Thompson, I. D., & Boccaccini, A. R. (2006). 45S5 Bioglass®-derived glass–ceramic scaffolds for bone tissue engineering. *Biomaterials*, *27*, 2414–2425. https://doi.org/10.1016/j.biomaterials.2005.11.025

Chung, C., & Burdick, J. A. (2008). Influence of three-dimensional hyaluronic acid microenvironments on mesenchymal stem cell chondrogenesis. *Tissue Engineering Part A*, *15*, 243–254.

Corbella, S., Taschieri, S., Weinstein, R., & Del Fabbro, M. (2016). Histomorphometric outcomes after lateral sinus floor elevation procedure: A systematic review of the literature and meta-analysis. *Clinical Oral Implants Research*, *27*, 1106–1122. https://doi.org/10.1111/clr.12702

D'Alessandro, D., Perale, G., Milazzo, M., Moscato, S., Stefanini, C., Pertici, G., & Danti, S. (2017). Bovine bone matrix/poly(L-lactic-co-e-caprolactone)/gelatin hybrid scaffold (SmartBone1) for maxillary sinus augmentation: A histologic study on bone regeneration. *International Journal of Pharmaceutics*, *523*, 534–544. https://doi.org/10.1016/j.ijpharm.2016.10.036

Damron, T. A. (2007). Use of 3D β-tricalcium phosphate (Vitoss®) scaffolds in repairing bone defects. *Nanomedicine (Lond)*, *2*, 763–775. https://doi.org/10.2217/17435889.2.6.763

Damron, T. A., Lisle, J., Craig, T., Wade, M., Silbert, W., & Cohen, H. (2013). Ultraporous beta-tricalcium phosphate alone or combined with bone marrow aspirate for benign cavitary lesions: Comparison in a prospective randomized clinical trial. *Journal of Bone and Joint Surgery-American*, *95*, 158–166. https://doi.org/10.2106/JBJS.K.00181

Datta, A., Gheduzzi, S., & Miles, A. W. (2006) A comparison of the viscoelastic properties of bone grafts. *Clinical Biomechanics (Bristol, Avon) 21*, 761–766. https://doi.org/10.1016/j.clinbiomech.2006.03.009 https://doi.org/10.1016/j.clinbiomech.2006.03.009

De Aza, A. H., Chevalier, J., Fantozzi, G., Schehl, M., & Torrecillas, R. (2002). Crack growth resistance of alumina, zirconia and zirconia toughened alumina ceramics for joint prostheses. *Biomaterials*, *23*, 937–945. https://doi.org/doi: 10.1016/S0142-9612(01)00206-X

de Grado, G. F., Keller, L., Idoux-Gillet, Y., Wagner, Q., Musset, A. M., Benkirane-Jessel, N., … Offner, D. (2018). Bone substitutes: A review of their characteristics, clinical use, and perspectives for large bone defects management. *Journal of Tissue Engineering*, *9*, https://doi.org/10.1177/2041731418776819

Delloye, C., Cornu, O., Druez, V., & Barbier, O. (2007). Bone allografts: What they can offer and what they cannot. *Journal of Bone and Joint Surgery. British Volume*, *89*, 574–579. https://doi.org/10.1302/0301-620X.89B5.19039

von Doernberg, M. C., von Rechenberg, B., Bohner, M., Grunenfelder, S., van Lenthe, G. H., Muller, R., … Auer, J. (2006). In vivo behavior of calcium phosphate scaffolds with four different pore sizes. *Biomaterials*, *27*, 5186–5198. https://doi.org/10.1016/j.biomaterials.2006.05.051

Dorati, R., DeTrizio, A., Modena, T., Conti, B., Benazzo, F., Gastaldi, G., & Genta, I. (2017). Biodegradable scaffolds for bone regeneration combined with drug-delivery systems in osteomyelitis therapy. *Pharmaceuticals (Basel)*, *10*, https://doi.org/10.3390/ph10040096

Ebraheim, N. A., Elgafy, H., & Xu, R. (2001). Bone-graft harvesting from iliac and fibular donor sites: Techniques and complications. *Journal of American Academy of Orthopaedic Surgeons*, *9*, 210–218. https://doi.org/10.5435/00124635-200105000-00007

Elliott, J. C. (2002). Calcium phosphate biominerals. Phosphates: Geochemical. *Geobiological, and Materials Importance*, *48*, 427–453. https://doi.org/DOI 10.2138/rmg.2002.48.11

El-Rashidy, A. A., Roether, J. A., Harhaus, L., Kneser, U., & Boccaccini, A. R. (2017). Regenerating bone with bioactive glass scaffolds: A review of in vivo studies in bone defect models. *Acta Biomaterialia*, *62*, 1–28. https://doi.org/10.1016/j.actbio.2017.08.030

Emara, K. M., Diab, R. A., & Emara, A. K. (2015). Recent biological trends in management of fracture non-union. *World Journal of Orthopedics*, *6*, 623–628. https://doi.org/10.5312/wjo.v6.i8.623

Epstein, N. E. (2013). Complications due to the use of BMP/INFUSE in spine surgery: The evidence continues to mount. *Surgical Neurology International*,*4*,S343–S352.https://doi.org/10.4103/2152-7806.114813

EUTCD (2004) Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of

quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cellsRetrieved from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM%3Ac11573.

Fielding, G. A., Bandyopadhyay, A., & Bose, S. (2012). Effects of silica and zinc oxide doping on mechanical and biological properties of 3D printed tricalcium phosphate tissue engineering scaffolds. *Dental Materials*, *28*, 113–122. https://doi.org/10.1016/j.dental.2011.09.010

Finkemeier, C. G. (2002a). Bone-grafting and bone-graft substitutes. *Journal of Bone and Joint Surgery-American*, *84*-A, 454–464. https://doi.org/10.2106/00004623-200203000-00020

Finkemeier, C. G. (2002b). Bone-grafting and bone-graft substitutes. *The Journal of Bone & Joint Surgery*, *84*, 454–464. https://doi.org/10.2106/00004623-200203000-00020

Fuchs, J. R., Nasseri, B. A., & Vacanti, J. P. (2001). Tissue engineering: A 21st century solution to surgical reconstruction. *Annals of Thoracic Surgery*, *72*, 577–591. https://doi.org/10.1016/S0003-4975(01)02820-X

Gaharwar, A. K., Mihaila, S. M., Swami, A., Patel, A., Sant, S., Reis, R. L., … Khademhosseini, A. (2013). Bioactive silicate nanoplatelets for osteogenic differentiation of human mesenchymal stem cells. *Advanced Materials*, *25*, 3329–3336. https://doi.org/10.1002/adma.201300584

Garcia-Gareta, E., Coathup, M. J., & Blunn, G. W. (2015). Osteoinduction of bone grafting materials for bone repair and regeneration. *Bone*, *81*, 112–121. https://doi.org/10.1016/j.bone.2015.07.007

Georgiou, G., & Knowles, J. C. (2001). Glass reinforced hydroxyapatite for hard tissue surgery—Part 1: Mechanical properties. *Biomaterials*, *22*, 2811–2815. https://doi.org/10.1016/s0142-9612(01)00025-4

Ghassemi, T., Shahroodi, A., Ebrahimzadeh, M. H., Mousavian, A., Movaffagh, J., & Moradi, A. (2018). Current concepts in scaffolding for bone tissue engineering. *The Archives of Bone and Joint Surgery*, *6*, 90–99.

Giannoudis, P. V., Chris Arts, J. J., Schmidmaier, G., & Larsson, S. (2011). What should be the characteristics of the ideal bone graft substitute? *Injury*, *42*(Suppl 2), S1–S2. https://doi.org/10.1016/j.injury.2011.06.001

Goldberg, V. M., & Akhavan, S. (2005) Biology of bone grafts. In: *Bone regeneration and repair* (pp. 57–65). Totowa, NJ: Humana Press. https://doi.org/10.1385/1592598633

Gomez-Florit, M., Rubert, M., Ramis, J. M., Haugen, H. J., Tiainen, H., Lyngstadaas, S. P., & Monjo, M. (2012). $TiO_2$ scaffolds sustain differentiation of MC3T3-E1 cells. *Journal of Biomaterials and Tissue Engineering*, *2*, 336–344. https://doi.org/10.1166/jbt.2012.1055

Grayson, W. L., Bunnell, B. A., Martin, E., Frazier, T., Hung, B. P., & Gimble, J. M. (2015). Stromal cells and stem cells in clinical bone regeneration. *Nature Reviews. Endocrinology*, *11*, 140–150. https://doi.org/10.1038/nrendo.2014.234

Hannink, G., & Arts, J. J. (2011). Bioresorbability, porosity and mechanical strength of bone substitutes: What is optimal for bone regeneration? *Injury-International Journal of the Care of the Injured*, *42*(Suppl 2), S22–S25. https://doi.org/10.1016/j.injury.2011.06.008

Haugen, H. J., Monjo, M., Rubert, M., Verket, A., Lyngstadaas, S. P., Ellingsen, J. E., … Wohlfahrt, J. C. (2013). Porous ceramic titanium dioxide scaffolds promote bone formation in rabbit peri-implant cortical defect model. *Acta Biomaterialia*, *9*, 5390–5399. https://doi.org/10.1016/j.actbio.2012.09.009

Hedberg, E. L., Kroese-Deutman, H. C., Shih, C. K., Crowther, R. S., Carney, D. H., Mikos, A. G., & Jansen, J. A. (2005). In vivo degradation of porous poly(propylene fumarate)/poly(DL-lactic-co-glycolic acid) composite scaffolds. *Biomaterials*, *26*, 4616–4623. https://doi.org/10.1016/j.biomaterials.2004.11.039

Hing, K. A. (2005). Bioceramic bone graft substitutes: Influence of porosity and chemistry. *International Journal of Applied Ceramic Technology*, *2*, 184–199. https://doi.org/DOI 10.1111/j.1744-7402.2005.02020.x

Hoffman, M. D., & Benoit, D. S. (2015). Agonism of Wnt-beta-catenin signalling promotes mesenchymal stem cell (MSC) expansion. *Journal of Tissue Engineering and Regenerative Medicine*, *9*, E13–E26. https://doi.org/10.1002/term.1736

Huang, Q.-W., Wang, L.-P., & Wang, J.-Y. (2014). Mechanical properties of artificial materials for bone repair. *Journal of Shanghai Jiaotong University (Science)*, *19*, 675–680. https://doi.org/10.1007/s12204-014-1565-8

Huiskes, R., Ruimerman, R., van Lenthe, G. H., & Janssen, J. D. (2000). Effects of mechanical forces on maintenance and adaptation of form in trabecular bone. *Nature*, *405*, 704–706. https://doi.org/10.1038/35015116

Hutmacher, D. W. (2006). Scaffolds in tissue engineering bone and cartilage. In: *The biomaterials: Silver jubilee compendium*. (pp. 175–189). Oxford, UK, Elsevier Science. https://doi.org/10.1016/B978-008045154-1/50021-6

Inzana, J. A., Olvera, D., Fuller, S. M., Kelly, J. P., Graeve, O. A., Schwarz, E. M., … Awad, H. A. (2014). 3D printing of composite calcium phosphate and collagen scaffolds for bone regeneration. *Biomaterials*, *35*, 4026–4034. https://doi.org/10.1016/j.biomaterials.2014.01.064

Jo, S. H., Kim, Y. K. & Choi, Y. H. (2018). Histological Evaluation of the Healing Process of Various Bone Graft Materials after Engraftment into the Human Body. *Materials*, *11*. doi:ARTN 71410.3390/ma11050714.

Jones, J. R., Ehrenfried, L. M., & Hench, L. L. (2006). Optimising bioactive glass scaffolds for bone tissue engineering. *Biomaterials*, *27*, 964–973. https://doi.org/10.1016/j.biomaterials.2005.07.017

Jung, U. W., Cha, J. K., Vignoletti, F., Nunez, J., Sanz, J., & Sanz, M. (2017). Simultaneous lateral bone augmentation and implant placement using a particulated synthetic bone substitute around chronic peri-implant dehiscence defects in dogs. *Journal of Clinical Periodontology*, *44*, 1172–1180. https://doi.org/10.1111/jcpe.12802

Karageorgiou, V., & Kaplan, D. (2005). Porosity of 3D biomaterial scaffolds and osteogenesis. *Biomaterials*, *26*, 5474–5491. https://doi.org/10.1016/j.biomaterials.2005.02.002

Kasten, P., Beyen, I., Niemeyer, P., Luginbuhl, R., Bohner, M., & Richter, W. (2008). Porosity and pore size of beta-tricalcium phosphate scaffold can influence protein production and osteogenic differentiation of human mesenchymal stem cells: An in vitro and in vivo study. *Acta Biomaterialia*, *4*, 1904–1915. https://doi.org/10.1016/j.actbio.2008.05.017

Kim, Y., Nowzari, H., & Rich, S. K. (2013). Risk of prion disease transmission through bovine-derived bone substitutes: A systematic review. *Clinical Implant Dentstry and Related Research*, *15*, 645–653. https://doi.org/10.1111/j.1708-8208.2011.00407.x

Knofler, W., Barth, T., Graul, R., & Krampe, D. (2016). Retrospective analysis of 10,000 implants from insertion up to 20 years-analysis of implantations using augmentative procedures. *International Journal of Implant Dentistry*, *2*, 25. https://doi.org/10.1186/s40729-016-0061-3

Kretlow, J. D., & Mikos, A. G. (2007). Review: Mineralization of synthetic polymer scaffolds for bone tissue engineering. *Tissue Engineering*, *13*, 927–938. https://doi.org/10.1089/ten.2006.0394

Lambert, F., Bacevic, M., Layrolle, P., Schupbach, P., Drion, P., & Rompen, E. (2017). Impact of biomaterial microtopography on bone regeneration: Comparison of three hydroxyapatites. *Clinical Oral Implants Research*, *28*, e201–e207. https://doi.org/10.1111/clr.12986

Larsson, S., & Hannink, G. (2011). Injectable bone-graft substitutes: Current products, their characteristics and indications, and new developments. *Injury-International Journal of the Care of the Injured*, *42*(Suppl 2), S30–S34. https://doi.org/10.1016/j.injury.2011.06.013

Laurencin, C., Khan, Y., & Veronick, J. (2014) Bone graft substitutes: Past, present, and future. In *Bone graft substitutes and bone regenerative engineering* (2nd ed.) (pp. 1–9). ASTM International: West Conshohocken, PA.

Lemons, J. E., Bajpai, P. K., Patka, P., Bonel, G., Starling, L. B., Rosenstiel, T., … Timmermans, J. (1988). Significance of the porosity and physical chemistry of calcium phosphate ceramics. Orthopedic uses. *Annals of the New York Academy of Sciences*, *523*, 278–282. https://doi.org/10.1111/j.1749-6632.1988.tb38521.x

Lo, K. W., Ashe, K. M., Kan, H. M., & Laurencin, C. T. (2012). The role of small molecules in musculoskeletal regeneration. *Regenerative Medicine*, *7*, 535–549. https://doi.org/10.2217/rme.12.33

Mano, J. F., Silva, G. A., Azevedo, H. S., Malafaya, P. B., Sousa, R. A., Silva, S. S., … Reis, R. L. (2007). Natural origin biodegradable systems in tissue engineering and regenerative medicine: Present status and some moving trends. *Journal of the Royal Society, Interface*, *4*, 999–1030. https://doi.org/10.1098/rsif.2007.0220

Mardas, N., Chadha, V., & Donos, N. (2010). Alveolar ridge preservation with guided bone regeneration and a synthetic bone substitute or a bovine-derived xenograft: A randomized, controlled clinical trial. *Clinical Oral Implants Research*, *21*, 688–698. https://doi.org/10.1111/j.1600-0501.2010.01918.x

Mardas, N., D'Aiuto, F., Mezzomo, L., Arzoumanidi, M., & Donos, N. (2011). Radiographic alveolar bone changes following ridge preservation with two different biomaterials. *Clinical Oral Implants Research*, *22*, 416–423. https://doi.org/10.1111/j.1600-0501.2010.02154.x

MarketReport (2015) Millenium Research Group Inc., Dental Biomaterials Europe Market Analysis. 175 Bloor St. East, South Tower, Suite 400, Toronto, Ontario, M4W 3R8, Canada: Millenium Research Group Inc.

MarketReport (2017) iData Research, Europe Market Overview for Dental Bone Graft Substitutes and Other Biomaterials 2017 - Research and Markets iData Research.

MarketReport (2018) Global Industry Analyst Inc., Bone graft substitute - globa strategic business report.

MDR (2017). Regulation (EU) 2017/745 of The European Parliament and of the Council of 5 April 2017 on medical devicesRetrieved: http://data.europa.eu/eli/reg/2017/2745/oj

Miao, X., Tan, D. M., Li, J., Xiao, Y., & Crawford, R. (2008). Mechanical and biological properties of hydroxyapatite/tricalcium phosphate scaffolds coated with poly(lactic-co-glycolic acid). *Acta Biomaterialia*, *4*, 638–645. https://doi.org/10.1016/j.actbio.2007.10.006

Miron, R. J., Zhang, Q., Sculean, A., Buser, D., Pippenger, B. E., Dard, M., … Zhang, Y. (2016). Osteoinductive potential of 4 commonly employed bone grafts. *Clinical Oral Investigations*, *20*, 2259–2265. https://doi.org/10.1007/s00784-016-1724-4

Müller, B. (2015) Bone-mimetic $TiO_2$ scaffolds with improved corrosion resistance. PhD thesis *Faculty of dentistry*. University of Oslo, Oslo, Norway.

Murata, K., Ito, H., Yoshitomi, H., Yamamoto, K., Fukuda, A., Yoshikawa, J., … Matsuda, S. (2014). Inhibition of miR-92a enhances fracture healing via promoting angiogenesis in a model of stabilized fracture in young mice. *Journal of Bone and Mineral Research*, *29*, 316–326. https://doi.org/10.1002/jbmr.2040

Murphy, C. M., Haugh, M. G., & O'Brien, F. J. (2010). The effect of mean pore size on cell attachment, proliferation and migration in collagen-glycosaminoglycan scaffolds for bone tissue engineering. *Biomaterials*, *31*, 461–466. https://doi.org/10.1016/j.biomaterials.2009.09.063

Novak, S., Druce, J., Chen, Q. Z., & Boccaccini, A. R. (2009). TiO2 foams with poly-(d, l-lactic acid) (PDLLA) and PDLLA/Bioglass(A (R)) coatings for bone tissue engineering scaffolds. *Journal of Materials Science*, *44*, 1442–1448. https://doi.org/10.1007/s10853-008-2858-9

Oliveira, A. L., Malafaya, P. B., & Reis, R. L. (2003). Sodium silicate gel as a precursor for the in vitro nucleation and growth of a bone-like apatite coating in compact and porous polymeric structures. *Biomaterials*, *24*, 2575–2584. https://doi.org/10.1016/S0142-9612(03)00060-7

Park, J. (2008) *Bioceramics: Properties, characterizations, and applications*. New York City, NY: Springer Science & Business Media.

Patel, K., Mardas, N., & Donos, N. (2013). Radiographic and clinical outcomes of implants placed in ridge preserved sites: A 12-month post-loading follow-up. *Clinical Oral Implants Research*, *24*, 599–605. https://doi.org/10.1111/j.1600-0501.2012.02500.x

Pei, M., Li, J. T., Shoukry, M., & Zhang, Y. (2011). A review of decellularized stem cell matrix: A novel cell expansion system for cartilage tissue engineering. *European Cells and Materials*, *22*, 333–343; discussion 343. https://doi.org/10.22203/eCM

Pertici, G., Rossi, F., Casalini, T., & Perale, G. (2014). Composite polymer-coated mineral grafts for bone regeneration: Material characterisation and model study. *Annals of Oral & Maxillofacial Surgery*, *2(1)*:4.

Pilipchuk, S. P., Plonka, A. B., Monje, A., Taut, A. D., Lanis, A., Kang, B., & Giannobile, W. V. (2015). Tissue engineering for bone regeneration and osseointegration in the oral cavity. *Dental Materials*, *31*, 317–338. https://doi.org/10.1016/j.dental.2015.01.006

Pilitsis, J. G., Lucas, D. R., & Rengachary, S. S. (2002). Bone healing and spinal fusion. *Neurosurgical Focus*, *13*, e1. https://doi.org/10.3171/foc.2002.13.6.2

Planell, J. A., Best, S., Lacroix, D., & Merolli, A. (2009) *Bone repair biomaterials*. Boca Raton, Fl.: CRC Press. https://doi.org/10.1533/9781845696610

Roato, I., Belisario, D. C., Compagno, M., Verderio, L., Sighinolfi, A., Mussano, F., … Ferracini, R. (2018). Adipose-derived stromal vascular fraction/xenohybrid bone scaffold: An alternative source for bone regeneration. *Stem Cells International*, *2018*, 4126379. https://doi.org/10.1155/2018/4126379

Roberts, T. T., & Rosenbaum, A. J. (2012). Bone grafts, bone substitutes and orthobiologics: The bridge between basic science and clinical advancements in fracture healing. *Organogenesis*, *8*, 114–124. https://doi.org/10.4161/org.23306

Rossi, F., Santoro, M., & Perale, G. (2015). Polymeric scaffolds as stem cell carriers in bone repair. *Journal of Tissue Engineering and Regenerative Medicine*, *9*, 1093–1119. https://doi.org/10.1002/term.1827

Rothermundt, C., Whelan, J., Dileo, P., Strauss, S., Coleman, J., Briggs, T., … Seddon, B. (2014). What is the role of routine follow-up for localised limb soft tissue sarcomas? A retrospective analysis of 174 patients. *British journal of cancer*, *110*, 2420. https://doi.org/10.1038/bjc.2014.200

Rubert, M., Pullisaar, H., Gomez-Florit, M., Ramis, J. M., Tiainen, H., Haugen, H. J., … Monjo, M. (2013). Effect of TiO2 scaffolds coated with alginate hydrogel containing a proline-rich peptide on osteoblast growth and differentiation in vitro. *Journal of Biomedical Materials Research Part A*, *101*, 1768–1777. https://doi.org/10.1002/jbm.a.34458

Sabetrasekh, R., Tiainen, H., Reseland, J. E., Will, J., Ellingsen, J. E., Lyngstadaas, S. P., & Haugen, H. J. (2010). Impact of trace elements on biocompatibility of titanium scaffolds. *Biomedical Materials*, *5*, 015003. https://doi.org/10.1088/1748-6041/5/1/015003

Saito, E., Saito, A., Kuboki, Y., Kimura, M., Honma, Y., Takahashi, T., & Kawanami, M. (2012). Periodontal repair following implantation of beta-tricalcium phosphate with different pore structures in class III furcation defects in dogs. *Dental materials journal*, *31*, 681–688. https://doi.org/10.4012/dmj.2011-259

Santos, F. A., Pochapski, M. T., Martins, M. C., Zenobio, E. G., Spolidoro, L. C., & Marcantonio, E. Jr (2010). Comparison of biomaterial implants in the dental socket: Histological analysis in dogs. *Clinical Implant Dentstry and Related Research*, *12*, 18–25. https://doi.org/10.1111/j.1708-8208.2008.00126.x

Sanz-Sanchez, I., Ortiz-Vigon, A., Sanz-Martin, I., Figuero, E., & Sanz, M. (2015). Effectiveness of lateral bone augmentation on the alveolar crest dimension: A systematic review and meta-analysis. *Journal of Dental Research*, *94*, 128s–142s. https://doi.org/10.1177/0022034515594780

Scarfi, S. (2016). Use of bone morphogenetic proteins in mesenchymal stem cell stimulation of cartilage and bone repair. *World J Stem Cells*, *8*, 1–12. https://doi.org/10.4252/wjsc.v8.i1.1

Schmidt-Rohlfing, B., Tzioupis, C., Menzel, C. L., & Pape, H. C. (2009). Tissue engineering of bone tissue. Principles and clinical applications. *Unfallchirurg*, *112*, 785–794; quiz 795. https://doi.org/10.1007/s00113-009-1695-x

Schroeder, J. E., & Mosheiff, R. (2011). Tissue engineering approaches for bone repair: Concepts and evidence. *Injury-International Journal of the Care of the Injured*, *42*, 609–613. https://doi.org/10.1016/j.injury.2011.03.029

Sinha, R., Menon, P. S., & Chakranarayan, A. (2009). Vitoss synthetic cancellous bone (Void Filler). *Medical Journal, Armed Forces India*, *65*, 173. https://doi.org/10.1016/S0377-1237(09)80136-6

St John, T. A., Vaccaro, A. R., Sah, A. P., Schaefer, M., Berta, S. C., Albert, T., & Hilibrand, A. (2003). Physical and monetary costs associated with autogenous bone graft harvesting. *American Journal of Orthopedics (Belle Mead NJ)*, *32*, 18–23.

Stacchi, C., Lombardi, T., Ottonelli, R., Berton, F., Perinetti, G., & Traini, T. (2018). New bone formation after transcrestal sinus floor elevation was influenced by sinus cavity dimensions: A prospective histologic and histomorphometric study. *Clinical Oral Implants Research*, *29*, 465–479. https://doi.org/10.1111/clr.13144

Stapleton, M., Sawamoto, K., Alméciga-Díaz, C. J., Mackenzie, W. G., Mason, R. W., Orii, T., & Tomatsu, S. (2017). Development of bone targeting drugs. *International Journal of Molecular Sciences*, *18*, 1345. https://doi.org/10.3390/ijms18071345

Tiainen, H., Wiedmer, D., & Haugen, H. J. (2013). Processing of highly porous $TiO_2$ bone scaffolds with improved compressive strength. *Journal of the European Ceramic Society*, *33*, 15–24. https://doi.org/10.1016/j.jeurceramsoc.2012.08.016

Tiainen, H., Wohlfahrt, J. C., Verket, A., Lyngstadaas, S. P., & Haugen, H. J. (2012). Bone formation in $TiO_2$ bone scaffolds in extraction sockets of minipigs. *Acta biomaterialia*, *8*, 2384–2391. https://doi.org/10.1016/j.actbio.2012.02.020

Vahle, J. L., Sato, M., Long, G. G., Young, J. K., Francis, P. C., Engelhardt, J. A., … Nold, J. B. (2002). Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1-34) for 2 years and relevance to human safety. *Toxicologic Pathology*, *30*, 312–321. https://doi.org/10.1080/01926230252929882

Verket, A., Tiainen, H., Haugen, H. J., Lyngstadaas, S. P., Nilsen, O., & Reseland, J. E. (2012). Enhanced osteoblast differentiation on scaffolds coated with $TiO_2$ compared to $SiO_2$ and CaP coatings. *Biointerphases*, *7*, 1–10.

Villa, O., Wohlfahrt, J. C., Mdla, I., Petzold, C., Reseland, J. E., Snead, M. L., & Lyngstadaas, S. P. (2015). Proline-rich peptide mimics effects of enamel matrix derivative on rat oral mucosa incisional wound healing. *Journal of Periodontology*, *86*, 1386–1395. https://doi.org/10.1902/jop.2015.150207

Vishwakarma, A., Sharpe, P., Shi, S., & Ramalingam, M. (2014) *Stem cell biology and tissue engineering in dental sciences*. London, UK: Academic Press.

Wang, Y., Kim, U. J., Blasioli, D. J., Kim, H. J., & Kaplan, D. L. (2005). In vitro cartilage tissue engineering with 3D porous aqueous-derived silk scaffolds and mesenchymal stem cells. *Biomaterials*, *26*, 7082–7094. https://doi.org/10.1016/j.biomaterials.2005.05.022

Wang, Y., Malcolm, D. W., & Benoit, D. S. W. (2017). Controlled and sustained delivery of siRNA/NPs from hydrogels expedites bone fracture healing. *Biomaterials*, *139*, 127–138. https://doi.org/10.1016/j.biomaterials.2017.06.001

Wheeler, D. L., & Enneking, W. F. (2005). Allograft bone decreases in strength in vivo over time. *Clinical Orthopaedics and Related Research*, 36–42.https://doi.org/10.1097/01.blo.0000165850.58583.50

Williams, D. F. (2008). On the mechanisms of biocompatibility. *Biomaterials*, *29*, 2941–2953. https://doi.org/10.1016/j.biomaterials.2008.04.023

Winkler, T., Sass, F. A., Duda, G. N., & Schmidt-Bleek, K. (2018). A review of biomaterials in bone defect healing, remaining shortcomings and future opportunities for bone tissue engineering THE UNSOLVED CHALLENGE. *Bone & Joint Research*, *7*, 232–243. https://doi.org/10.1302/2046-3758.73.Bjr-2017-0270.R1

Wu, C., Luo, Y., Cuniberti, G., Xiao, Y., & Gelinsky, M. (2011). Three-dimensional printing of hierarchical and tough mesoporous bioactive glass scaffolds with a controllable pore architecture, excellent mechanical strength and mineralization ability. *Acta Biomaterialia*, *7*, 2644–2650. https://doi.org/10.1016/j.actbio.2011.03.009

Xavier, J. R., Thakur, T., Desai, P., Jaiswal, M. K., Sears, N., Cosgriff-Hernandez, E., … Gaharwar, A. K. (2015). Bioactive nanoengineered hydrogels for bone tissue engineering: A growth-factor-free approach. *ACS Nano*, *9*, 3109–3118. https://doi.org/10.1021/nn507488s

Yamada, M., & Egusa, H. (2018). Current bone substitutes for implant dentistry. *Journal of Prosthodontic Research*, *62*, 152–161. https://doi.org/10.1016/j.jpor.2017.08.010

Yan, J., Li, J., Runge, M. B., Dadsetan, M., Chen, Q., Lu, L., & Yaszemski, M. J. (2011). Cross-linking characteristics and mechanical properties of an injectable biomaterial composed of polypropylene fumarate and polycaprolactone co-polymer. *Journal of Biomaterials Science, Polymer Edition*, *22*, 489–504. https://doi.org/10.1163/092050610X487765

Yang, G. J., Lin, M., Zhang, L., & Gou, Z. R. (2013). Progress of calcium sulfate and inorganic composites for bone defect repair. *Journal of Inorganic Materials*, *28*, 795–803. https://doi.org/10.3724/Sp.J.1077.2013.12758

Zimmermann, G., & Moghaddam, A. (2011). Allograft bone matrix versus synthetic bone graft substitutes. *Injury-International Journal of the Care of the Injured*, *42*, S16–S21 https://doi.org/10.1016/j.injury.2011.06.199

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