Synthetic Biomaterials, Alveolar Bone Regeneration

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Contributor: Matej Tomas

The alveolar process is the thick bone ridge that contains the tooth sockets. The alveolar bone is located on the teeth-holding jaw bones.

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1. Overview

After tooth extraction, the alveolar ridge undergoes dimensional changes. Different bone regeneration biomaterials are used to reduce bone loss. The aim of this article was to systematically review the literature on the effect of injectable synthetic biomaterials and their advantages and disadvantages for new bone formation in the maxilla and mandible in animals and humans. A literature search was conducted in November 2020 via MEDLINE PubMed, Cochrane, and Embase. Of the 501 records screened, abstract analysis was performed on 49 articles, resulting in 21 studies that met the inclusion criteria. Animal studies have shown heterogeneity in terms of animal models, follow-up time, composition of the injectable biomaterial, and different outcome variables such as bone–implant contact, newly formed bone, and peri-implant bone density. Heterogeneity has also been demonstrated by human studies. The following outcomes were observed: newly formed bone, connective tissue, residual injectable bone graft substitute, radiographic density, residual bone height, and different follow-up periods. Further studies, especially in humans, based on the histological and biomechanical properties of the injectable delivery form, are needed to draw more concrete conclusions that will contribute to a better understanding of the benefits of this type of biomaterials and their role in bone regeneration.

2. Different Materials for Bone Regeneration

In cases of atrophy of the alveolar ridge or localized bone defects in the long term, peri-implant hard and soft tissues are disturbed. Alveolar resorption after tooth extraction occurs in the first year. Previous human studies have described horizontal bone loss of 29–63% and vertical bone loss of 11–22% during the first 6 months after tooth extraction. In addition, when the height of the alveolar ridge is more than 5 mm, procedures such as augmentation and implant placement can be performed simultaneously, as opposed to cases in which the height of the residual ridge is less than 5 mm and requires time for bone healing after biomaterial insertion and final implant placement. Nowadays, many different bone regeneration biomaterials such as allografts, xenografts, autogenous bone, and synthetic biomaterials are used to reduce dimensional changes of the alveolar ridge and stimulate bone regeneration [1][2][3]. The following flowchart shows the different biomaterials used in dental medicine for bone regeneration (Figure 1).

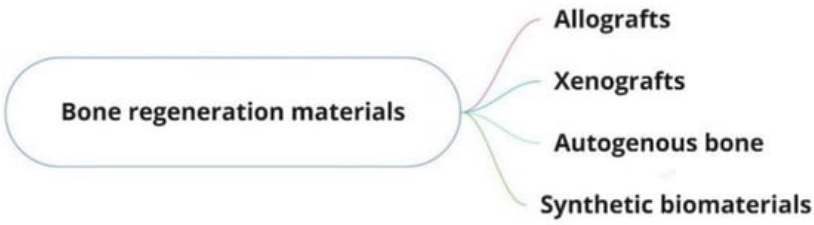

Figure 1. Flowchart of different bone regeneration biomaterials.

2.1. Allografts

The source of an allogeneic bone graft is an individual (i.e., a living donor or a cadaver) of the same species but of a different genotype. The advantages of this biomaterial are avoidance of a secondary surgical site and shortened procedure time. Some of the disadvantages of allogeneic grafts are infection, nerve damage at the donor site, and limited bone availability [4].

2.2. Xenografts

Xenografts are bone substitutes derived from animals such as cattle, pigs, and horses. Prior to use, such bone must undergo a mechanical and chemical purification process to remove organic components and eventually yield hydroxyapatite granules that closely resemble human bone. Xenografts are biocompatible and hydrophilic and have osteoconductive properties. Theoretically, bovine xenografts pose a risk of transmitting prion infections to the recipient, which is one of the disadvantages of this biomaterial. Research has shown that the risk of transmission of disease is negligible, but suspicion still exists. Xenografts are available in the form of bone blocks or granules (grafts made of small or large particles). Another disadvantage is that a xenogeneic bone block may fracture during fixation, affecting the surgical procedure and bone healing. Xenografts are used in the following cases: cavity preservation, sinus floor augmentation, and guided bone regeneration. In addition, due to their advantages in terms of mechanical properties and resorption resistance, they are often combined with autogenous bone to achieve volume stability [5][6][7][8].

2.3. Autogenous Bone

Autogenous bone is considered the gold standard for clinical bone augmentation. The material is completely biocompatible because the donor is the patient himself/herself. For this reason, an additional surgical site is needed from which the replacement is taken; this site can be intraoral or extraoral. One of the main problems with autogenous bone graft is resorption. The graft has a tendency to lose volume (40%) during healing and remodeling. Other shortcomings such as a different surgical site, limited availability, morbidity, risk of bleeding, edema, and postoperative pain have led to the development of new biomaterials [7][9][10][11][12][13][14][15].

2.4. Dentin Matrix

The first documented evidence of the osteoinductive potential of a demineralized dentin matrix was provided in 1967 by the detection of bone morphogenetic proteins (BMPs) in dentin [16]. Bone morphogenetic proteins belong to the TGF-β family and are the only signaling molecules that can independently induce de novo bone formation at orthotopic and heterotopic sites, and their presence in dentin primarily distinguishes them from xenogeneic biomaterials that do not contain proteins [11][17][18]. In 2003, dentin was first used clinically as an augmentation material in maxillary sinus augmentation [19]. Since 2008, dentin has been increasingly used as an augmentation material thanks to the development of devices that facilitate its clinical use [20].

In addition to BMPs, dentin contains both type I and type III collagen, as well as other growth factors, including insulin-like growth factor 2 (IGF-II) and transforming growth factor β (TGF-β) [21][22]. Most bone remodeling proteins such as osteopontin (OPN), osteocalcin (OCN), bone sialoprotein (BSP), osterix, type I collagen, and Cbfa1 (Runx2) have also been identified in dentin, making it an effective bone substitute [23][24][25][26].

2.5. Synthetic Biomaterials

Alloplastic bone grafts, which belong to the group of synthetic biomaterials, are used as an alternative to the gold standard. Advantages of these bone graft substitutes are their biocompatibility, osteoconductive capabilities, and stability. In addition, no donor site is required, and there is no risk of transmission of infectious diseases [21][22][23].

Synthetic bone substitutes represent a large group of inorganic biomaterials with different physical, chemical, and structural properties. Synthetic bone substitutes are composed of calcium phosphate to be as similar as possible to natural bone, which is mainly composed of calcium phosphate hydroxyapatite. The first experimental use of these biomaterials was reported in the 1920s [24]. Synthetic calcium phosphates include non-resorbable, rigid, friable hydroxyapatite (HA), resorbable β-tricalcium phosphate (β-TCP), and a complex called biphasic calcium phosphate (BCP) [9][24]. The HA does not resorb but acts as a scaffold to maintain space and integrity in the host bone defect, while β-TCP is fully resorbed, resulting in the stimulation of new bone through the release of calcium and phosphorus ions [24][25][26].

Synthetic biomaterials must be such that they do not cause inflammation and an inflammatory response. A proper balance between resorption of the scaffold and new bone formation is important for successful bone remodeling [9]. In addition, the integration of biomaterials and their degradation and vascularization may be influenced by the amount of cytokine and invasive inflammatory cell secretion. When tissue is damaged and the biomaterial is incorporated into the defect, inflammatory mediators are released from protein plasma and tissue, which adhere to the biomaterial. Such a cell layer leads to the integration of inflammatory mediators, of which macrophages should be highlighted, which are involved in the degradation and/or phagocytosis of the introduced biomaterial. In addition, depending on the size of the material the macrophages come into contact with, the overall cellular inflammatory response and granulation tissue formation are

affected. Larger particles of size >500 µm with low porosity lead to better bone regeneration as they degrade more slowly than particles of size <50 µm. Therefore, in a study by Karabuda et al., in which three different biomaterials were used, the relationship between new bone formation and resorption of a particular biomaterial was observed. The results showed that the biomaterial with granules of size from 500 to 1000 µm contributed to a higher percentage of newly formed bone. In the same study, biomaterials with a smaller granule size were histologically found to have the most connective and marrow tissue after 6 months of healing. However, smaller particles allow filling of all defects and cannot prevent the ingrowth of connective tissue into the defect due to their rapid degradation. Therefore, according to Ghanaati et al., in purely synthetic biomaterials, incorporation of pure ß-TCP granules into the aqueous carrier system could prevent rapid degradation of biomaterials, especially in injection pastes where the granules are a bioactive filler and the aqueous phase contributes to material integrity as a carrier. Therefore, changes in the porosity, morphology, and particle size of a given biomaterial may affect the final result [3][27][28].

Various forms of CaP biomaterials exist on the market as powders, blocks, and granules in many sizes, which are difficult to handle, especially when applying bone material into three-dimensional cavities. These disadvantages have led to the development of materials in injectable form [21][29]. In addition, the increasing use of biomaterials in injectable form has become popular due to their viscosity and ease of use. This can lead to a better clinical outcome and a reduction in surgical time [21][30].

However, various clinical cases require the use of injectable bone substitutes (IBS) with certain additives. Most IBS are based on hydrophilic polymers such as collagen, hyaluronic acid (HY), and cellulose, in addition to calcium-phosphate-based granules. In a study by Barbeck et al., it was shown that the addition of HY and methylcellulose to β-TCP granules results in a biomaterial that plays an integrative role by inducing continuous cell growth from the periphery to the core, thus increasing vascularization around the implant [22]. In addition, authors of studies conducted on animal (Struillou et al. 2011) and human models (Weiss et al., 2007) support that the adjunction of silanized hydroxypropylmethylcellulose (Si-HPMC) interacts as a cohesive factor for BCP granules and contributes to better osteoconductive properties of the biomaterial and eventually to an excellent clinical outcome [31][32].

CaP cements without any additives usually show poor injectability due to liquid separation and a solid phase. In most cases, purely inorganic CaP pastes tend to disintegrate in the early stages of contact with biological fluids (blood) due to poor cohesion. Finally, the release of calcium phosphate particles into the bloodstream can cause certain complications; increased blood clotting can lead to disorders in the cardiovascular system causing, for example, pulmonary embolism. Numerous studies have been devoted to improving the aforementioned injection form of CaP cement by varying various factors such as composition, particle size, liquid-to-powder ratio, and processing during preparation. Moreover, many organic or inorganic additives such as citric acid, cytosan, gelatin, collagen, sodium alginate, polymer fibers, and their impurities are added to the powder or liquid phase to improve the handling and mechanical properties [33]. A parallel can be drawn to the study by Mai et al. (2012), conducted on an animal model, in which the combination of injectable calcium phosphate cement with polylactic co-glycolic acid (PLGA) improved the properties of the injectable biomaterial for the purpose of bone regeneration. In addition, in a study by Hoekstra et al. (2013), the addition of PLGA resulted in porosity, which increased the surface area of the CaP cement and ultimately led to direct contact of the biomaterial with the bone without soft-tissue intervention [17][34].

These studies show that even small amounts of certain additives can improve the injection properties and cohesion of CaP cement.

We can divide CaP cements into single-phase and two-phase cements. In general, single-phase CaP cements in injectable form are biocompatible and osteoconductive, but their degradation is generally slow. As noted in many animal studies, e.g., Guha et al. and Felix et al., the addition of polymeric microparticles is useful to increase the cement degradation rate.

This is based on the fact that the degradation rate of sintered low-solubility cements can be significantly accelerated by introducing a secondary-phase CaP with higher solubility, such as ß-tricalcium phosphate (ß-TCP). Two-phase CaP cements consisting of α and ß components were shown to contribute to bone formation in a study by Jansen et al. Cements consisting of 85% α-TCP and 15% ß-TCP contributed to bone formation. Parallels can be drawn here with a study by Sariibrahimoglu et al., in which the two-phase nature of cements was compared. Two-phase CaP cement showed a better curing time and injectability compared to single-phase CaP cement. Further in vitro studies on this topic are needed to analyze the differences [29][35][36][37].

Thus, the main advantage of injectable forms of CaP cements compared to CaP cements in other forms is that they can be placed in the bone cavity by themselves without mechanical processing. This feature is important in clinical applications with various wider or narrower bone defects, which favors the further development of minimally invasive surgical procedures.

Knowing all this, alloplastic biomaterials and their design, i.e., use with syringes of various sizes, have become increasingly popular and are an ideal substitute for other types of biomaterials, with the ability to cover the borders of various defects in the oral cavity and, thus, increased osteoconductive properties. Animal and human studies on these injectable biomaterials play an important role in the field of dentistry [30][33][38].

The aim of this article was to systematically review the literature on the effects of injectable synthetic biomaterials and their advantages and disadvantages for new bone formation in the maxilla and mandible in animals and humans.

3. Conclusions

The conclusions that can be drawn suggest that bone augmentation with injectable biomaterials increases bone volume and allows adequate implant placement in the atrophic maxilla and mandible. The injectable form of the biomaterial offers a modern way of insertion into the defect; more specifically, it can be adapted immediately after implant placement in three-dimensional defects and thus fits precisely into the defects, unlike other forms that are usually in the form of a block and need to be specifically adapted to each individual defect before insertion. Based on animal and human studies reviewed in this paper, the advantages of the injectable form of biomaterials are better handling and application to smaller defects in terms of delivery to hard-to-reach sites, reduction in surgical time, compressive strength, favorable tissue response, rapid resorption associated with the use of smaller particles with the formation of new bone, and the ability to mix the biomaterial with various additives that increase interaction between cells.

However, the disadvantages of injectable forms of biomaterials include the inability to use them in geometrically challenging large cavities that require the use of solid biomaterials due to larger granules, increased viscosity due to higher liquid content, and consequently more difficult injection and leakage. Due to all these points, further studies, especially in humans, based on histological and histomorphological analyses of biomaterials, with a better understanding of the biomechanical properties of injectable form delivery, are needed to draw more concrete conclusions that will contribute to a better understanding of the performance of this type of biomaterials and their role in alveolar bone regeneration.

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