Bone grafting materials in dentoalveolar reconstruction: A comprehensive review

S. Titisnides a, *, G. Agrogiannis b, T. Karatzas c

a Department of Oral Medicine and Pathology, Dental School, University of Athens, Athens, Greece
b 1st Department of Pathology, Medical School, University of Athens, Athens, Greece
c 2nd Department of Propedeutic Surgery, Laiko General Hospital, Medical School, University of Athens, Athens, Greece

Abstract

Bone deficits of the jaws are often attributed to accidents, surgical removal of benign lesions or malignant neoplasms, congenital abnormalities, periodontal inflammation, tooth abscess or extraction and finally jaw atrophy due to advanced age or general disease.

These bone defects require rehabilitation for a variety of reasons, e.g. maintaining the normal anatomic outline, eliminating empty space, aesthetic restoration and placing dental implants. Today, several techniques have been developed to eliminate these bone deformities including bone grafting, guided bone regeneration, distraction osteogenesis, use of growth factors and stem cells.

Bone grafts consist of materials of natural or synthetic origin, implanted into the bone defect site, documented to possess bone healing properties. Currently, a variety of bone restorative materials with different characteristics are available, possessing different properties.

Despite years of effort the 'perfect' bone reconstruction material has not yet been developed, a further effort is required to make this objective feasible.

The aim of this article is to provide a contemporary and comprehensive overview of the grafting materials that can be applied in dentoalveolar reconstruction, discussing their properties, advantages and disadvantages, enlightening the present and the future perspectives in the field of bone regeneration.

© 2018 The Authors. Published by Elsevier Ltd on behalf of The Japanese Association for Dental Science. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Bone deficits of the jaws are often attributed to accidents (traffic, labor, sports, shooting), surgical removal of benign lesions (cysts, dental tumors) or malignant neoplasms, congenital abnormalities such as clefts or visceral skull bones hypoplasia, periodontal inflammation, tooth abscess or extraction and finally jaw atrophy due to advanced age or general disease [1].

With the advancements in the field of dentoalveolar reconstruction, these jaw bone defects are capable of rehabilitation for a variety of reasons, e.g. maintaining the normal anatomic outline, eliminating empty space, aesthetic restoration and placing dental implants [2]. Today, several techniques have been developed to eliminate these bone deformities including bone grafting, guided bone regeneration, distraction osteogenesis, use of growth factors and stem cells [3].

Bone grafts consist of materials of natural or synthetic origin, implanted into the bone defect site, documented to possess bone healing properties. Currently, a variety of bone restorative materials with different characteristics are available, classified in various categories according to histologic architecture, embryologic origin, form and blood supply, as shown in Table 1. With regards to their source of origin bone grafts are divided into the following types (Table 2): 1. Autografts obtained from the patient itself, possessing no antigenic properties since the donor and the recipient are the same person; 2. Isografts derived from the same species and share the same antigenic properties (twins); 3. Allografts processed in an effort to eliminate antigenic properties since the donor and the recipient is a different person of the same species; 4. Xenografts obtained from different species to humans; 5. Synthetic bone graft substitutes developed to mimic the natural bone tissue [2,4].

Materials of various origin and composition have different bone regeneration potential associated with the following properties: 1. Osteogenesis: living osteoblasts derived from the graft contribute

---

* Corresponding author at: 3 Argolidos Street, Athens 11523, Greece.
E-mail address: titisnides@yahoo.com (S. Titisnides).

https://doi.org/10.1016/j.jdsr.2018.09.003
1882-7616/© 2018 The Authors. Published by Elsevier Ltd on behalf of The Japanese Association for Dental Science. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
to the production of new bone; 2. Osteoinduction: stimulation of osteoprogenitor cells that differentiate into osteoblasts, usually influenced by a bone morphogenetic protein (BMP) released from the graft; 3. Osteoconduct: grafts provide a ‘skeleton’ aiding capillaries and precursor bone cells to develop, thus creating a scaffold which bone can be created in and around [5].

The ideal material for bone rehabilitation should possess the following characteristics: 1. Osteogenic, osteoinductive and osteoconductive properties; 2. Stimulation of neo-angiogenesis; 3. Lack of antigenic, teratogenic or carcinogenic reactions; 4. Supply in sufficient quantities; 5. Satisfactory support and stability; 6. Minimum to zero morbidity — complications; 7. Hydrophilic nature; 8. Easy handling; 9. Low cost [6].

Despite years of effort the ‘perfect’ bone reconstruction material has not yet been developed, a further effort is required to make this objective feasible.

The aim of this article is to provide a contemporary and comprehensive overview of the grafting materials that can be applied for bone reconstruction in dentoalveolar reconstruction, discussing their properties, advantages and disadvantages, enlightening the present and the future perspectives in the field of bone regeneration.

### 2. Bone grafting physiology

Bone is a specialized, mineralized tissue providing structural support and participating in calcium metabolism homeostasis of the organism. It consists of inorganic minerals and organic components, incorporating cells that produce and absorb bone constantly, in the context of bone remodeling.

Integration of the graft into the recipient site is a procedure that includes the following stages: inflammation, revascularization, osteoinduction, osteoconduct and finally remodeling. To achieve bone regeneration, bone grafts should exhibit three fundamental elements: 1. Osteoprogenitor mesenchymal cells or even living osteoblasts; 2. Growth factors that are beneficial for the regenerative process; and 3. A ‘skeleton’ capable of mechanically supporting adhesion of cells, further leading to their growth and proliferation [7].

Mesenchymal cells further differentiating or even mature osteoblasts are likely to be present within the bone graft structure as in the case of osteogenic materials.

Growth factors represent a variety of molecules that stimulate mesenchymal cells recruitment, proliferation and differentiation from the surrounding environment into the bone deficit. Bone tissue is a rich source of growth factors, including BMPs, platelet-derived growth factor, insulin-like growth factor–1, vascular endothelial growth factor and fibroblast growth factor. The BMP family is considered to be the most important group of molecules of this category including members like BMP–2, 4, 6, 7 that exhibit satisfactory bone growth [8]. Bone grafts possessing such molecules are characterized as osteoinductive.

Finally, the skeleton — scaffold is represented by the bone graft, regardless of its biological origin. Its function is to recreate a three-dimensional mechanical structure that hosts and supports cells and extra-cellular matrix. Porous elements are essential for the

### Table 1

Classification of bone grafting materials by selection of different criteria.

| Source       | Histologic architecture | Embryologic origin | Blood supply | Form of the graft |
|--------------|-------------------------|--------------------|--------------|-------------------|
| Autologous   | Cortical                | Endochondral       | Free graft   | Bone blocks       |
| Allografts   | Cancellous              | Membranous         | Regional flap| Particulate bone  |
| Xenografts   | Corticocancellous       |                    |              | Bone slurry       |
| Allografts   |                        |                    |              | Bone paste        |

### Table 2

Bone grafts classified according to their source of origin.

| Graft category | Graft type                        | Advantages                                               | Disadvantages                                      | Commercially available |
|---------------|-----------------------------------|----------------------------------------------------------|----------------------------------------------------|------------------------|
| Autografts    | Extra-oral: Cranium, Fibula, iliac crest, Radius, Rib, Tibia | Osteogenic Osteoinductive Osteoconductive No disease transmission or immunogenicity | Donor site morbidity Limited quantity Possibility of general anaesthesia and hospitalization (for extra-oral sites) | Allograft, DBX, DynaBlast, Dynagraft, Grafton, MTF, Opteform, OsteoSponge, Puros, Raptos |
| Allografts    | Fresh and/or frozen bone Freeze dried bone Demineralized freeze dried bone | Osteoinductive Osteoconductive Relative availability | Possibility of disease transmission and immunogenicity Variability of properties depending on productive method | Allograft, DBX, DynaBlast, Dynagraft, Grafton, MTF, Opteform, OsteoSponge, Puros, Raptos |
| Xenografts    | Bovine Porcine Equine Coralline Algae | Osteoinductive Osteoconductive High availability Low cost Possibility of disease transmission and immunogenicity Variability of properties depending on productive method | Possibility of disease transmission and immunogenicity Variability of properties depending on productive method | Allograft, DBX, DynaBlast, Dynagraft, Grafton, MTF, Opteform, OsteoSponge, Puros, Raptos |
| Synthetic bone substitutes | Calcium phosphate Hydroxyapatite Calcium carbonate Calcium sulphate HTR polymer Bioactive glasses | Osteoinductive Availability Low cost | Variability of properties depending on productive method | Biogran, BonePlast, Calbone, Cortoss, Eurobone, Guidor easy-graft, Hydroset, InjeniOs, Macrobone, Ostini, Perioglass, Rhakos, Straumann, Vitoss, |
formation of the scaffold, allowing migration and proliferation of osteoblasts, mesenchymal cells and neo-vascularization while they accelerate biodegradation of the material by increasing contact with body fluids [9]. Osteoblasts are thought to perform greater migration, adhesion, and proliferation in the presence of pores with a diameter of 200–400 mm, while when greater than 300 mm, more intense vascular formation occurs. Generally, researchers suggest a porosity of more than 50% by volume and pore sizes between 200 and 800 mm as optimal for the development of bone tissue [10,11]. Apart from pore size, other parameters like pore morphology, pore percentage and pore interconnectivity seem to be important [12]. These grafting properties are defined as osteoconductive, as described above.

Cortical and cancellous bone histology of the grafts plays a significant role in their biologic behavior that can be summarized into the following: 1. Cancellable grafts stimulate osteogenesis given the presence of osteoblasts, osteocytes and mesenchymal stem cells within its structure; 2. Stability is mainly provided by cortical grafts which are significantly deficient in osteogenic ability, exhibit extended absorption while new bone growth is very slow; 3. A combination of cortical and cancellous grafts can ensure stability and osteogenesis; 4. Differences also exist in mechanical strength that is increased in cancellous bones due to the faster deposition rate of new bone tissue, while in the cortical grafts mechanical strength decreases by 40% from the first 6 weeks to 6 months post-operatively [13]. Cortical substitutes are usually applied as onlay grafts, augmenting bone outside the anatomical boundaries of the skeleton while they can also be used for inlay bone healing. In general, onlay bone grafts exhibit a higher resorption rate since they are exposed less in the recipients’ site vasculature and they accept forces from the surrounding soft tissues compared to inlay grafting. Cancellous grafts are commonly used in fracture non-union, lack initial mechanical strength but exhibit ease during intra-operative manipulations [14].

Vascularized bone grafts seem to be more reliable in cases with previous radiation therapy of the bone and intense deficiency of soft and/or bone tissues. Among their drawbacks, high cost, the need for specialized training and equipment, as well as relatively more donor site morbidity have to be considered [15].

Bone grafts exhibit different absorption during time due to material composition, particle size, crystallinity, porosity, and processing procedure. The absorption rate of the material should ideally be proportional to the formation of the new bone.

Successful integration of the graft material is the constituent of factors such as adequate revascularization, proper fixation — immobilization at the recipient site, soft tissue coverage, appropriate shaping of the grafts’ surface to establish relative contact with the recipient site, application of aseptic technique by the surgeon, meticulous post-operative care, while details from patients’ medical history such as prior irradiation of the area as well use of drugs that are likely to cause osteonecrosis of the jaws should be considered [16].

A comprehensive description of the various categories of bone grafting materials is following below.

2.1. Bone grafts

2.1.1. Autografts

Autografts are considered the ‘gold standard’ among the various available grafting materials due to their osteogenic properties, maintaining viable cells from the donor to the recipient site as well as osteoinductive characteristics since a variety of growth factors contribute to the differentiation of mesenchymal stem cells into osteoblasts. The fact that they share the same biological origin with the host organism makes the risk of an immune reaction — rejection zero, acquiring success rate >95% [17,18]. The creation of a second trauma, sometimes affecting even the patient’s systemic health and increased morbidity, especially in cases of extensive bone volume collected, counts on their drawbacks. Also, limited bone offer is described, especially when intraoral graft sites are selected, as well as possibility of chronic postoperative pain and hypersensitivity of the donor area [19]. A variety of intra- and extra-oral donor sites have been described for the repair of jaw bone deficits. Intra-oral bone harvesting possesses the following advantages over extra-oral areas: ease of surgical access, relative proximity between the donor and the recipient site, lack of permanent skin scarring and minimal post-operative morbidity [20]. In addition, membranous ossification of the maxilla and mandible appears to play an important role in their absorption rate that is lower compared to the bones of endochondral ossification as well as better integration because they contain higher concentration of growth factors and angiogenetic potential [21]. However, according to other authors, these observations are mainly attributed to the micro-architecture of the graft, in particular the ratio between cortical and cancellous bone versus their embryonic origin [7,22].

Regarding grafts derived from extra-oral regions, they are considered to provide larger graft volumes, which may affect the decision of the clinician, especially in cases of large bone deficiency repair. In such cases need for general anaesthesia, hospitalization, increased morbidity are expected in combination with clinicians’ advanced training [17].

The final decision for the selection of the donor site is determined by the particularities of the bone deficit to be restored, doctor’s personal experience and preferences as well as the acceptance of the therapeutic plan by the patient.

At the moment numerous autografting donor sites have been described but since their detailed description overweighs the limits of this review a concise summary of available intra- and extra-oral regions for autogenous bone harvesting is provided on Table 3 [23–38].

2.1.2. Allografts

Allografts derive from individuals of the same species but different genus, being selected, processed and preserved in bone banks where extensive donor screening, including detailed social and medical history as well as serological examinations is carried out. They originate from living donors (usually femoral head replacement) or cadaveric bone material, further processed to neutralize the immune response and transmission of infectious diseases [39]. They are available as cortical, cancellous or cortico-cancellous grafts, in various shapes and sizes.

The main types of these materials comprise: 1. Fresh frozen bone (FFB): frozen at −800°C to avoid degradation by enzymes, without further irradiation, lyophilization or demineralization process. It is acellular, possessing the highest osteoinductive and osteoconductive properties due to the presence of BMPs. Not used anymore due to disease transmission and high immune response [40]; 2. Freeze–dried bone allograft (FDDB): undergone dehydration and freezing without demineralization, leading to decreased antigenicity. It has only osteoconductive potential; 3. Demineralized freeze–dried bone allograft (DFDBA): apart from dehydration, the inorganic part of the bone is eliminated, leaving only the organic part that contains BMPs. These materials exhibit osteoconductive and inductive features [4,41].

The advantages of allografts include availability in adequate quantities, sizes and shapes, predictable results and the elimination of an additional donor site surgery. On the other hand, disease transmission from the donor to the recipient, although extremely small, cannot be totally excluded and additional testing for HIV, Hepatitis B virus, Hepatitis C virus and Treponema serologic markers should be performed [42]. It must be also noted
Table 3
Available intra- and extra-oral sites for bone harvesting.

| Graft type      | Advantages                          | Disadvantages                        | Complications |
|-----------------|-------------------------------------|--------------------------------------|---------------|
| A. EXTRA – ORAL |                                     |                                      |               |
| Cranium [23]    | Slow resorption                     | Mainly cortical bone                 | Dural injuries |
|                 | High stability                       | Need for general anaesthesia         | Epidural hematoma |
|                 | Low donor site morbidity             |                                      | Alopecia      |
|                 | Large quantities harvesting         |                                      |               |
|                 | Scar hidden by hair                 |                                      |               |
| Fibula [24]     | Large quantities harvesting         | Long incision                        | Partial restriction of joint motions |
|                 | Corticocancellous graft             | Need for general anaesthesia         | Ankle instability |
|                 | Ideal for onlay grafting            |                                      | Muscular weakness |
|                 |                                      |                                      | Long scar     |
| Iliac crest [25] | Large quantities harvesting         | 12%–60% resorption rate of the initial bone graft | Pelvic instability |
|                 | Ideal for onlay grafting            |                                      | Fatigue fracture |
|                 |                                      |                                      | Iliac hernia  |
|                 |                                      |                                      | Fistula       |
|                 |                                      |                                      | Ureteral injury |
|                 |                                      |                                      | Heterotopic bone formation |
| Radius [26]     | Corticocancellous graft             | Limited bone quantity                | Superior soft-tissue infection Fracture |
|                 | No need for general anaesthesia     |                                      | DeQuervain's tenosynovitis |
| Rib [27]        | Can be splitted to double the surface area of the graft | Mainly cortical bone                | Pneumothorax  |
|                 | Rib donor area can regenerate       |                                      | Chest wall depression |
|                 | Adequate bone length that can bridge large defects |                                      | Pleuritic pain |
| Tibia [28]      | Large quantities of cancellous bone | Cancellable bone gained of inferior quality compared to iliac crest | Gait disturbance |
|                 | Local anaesthesia possible Minimal scar |                                      | Entrance into joint space |
|                 |                                      |                                      | Edema         |
|                 |                                      |                                      | Paresthesia   |
|                 |                                      |                                      | Tibial fracture |
| B. INTRA – ORAL |                                     |                                      |               |
| Anterior maxillary sinus wall [29] | Recipient site in proximity | Mainly cortical bone                 | Perforation of Schneiderian membrane |
|                 | Low resorption                      |                                      |               |
| Anterior nasal spine [30] | Easy bone harvesting | Limited bone quantity                | Basement membrane perforation |
|                 | Low morbidity                       |                                      | Aesthetic alterations |
| Ascending ramus [31] | Preferred by patients compared to | Mainly cortical bone                 | Damage of inferior alveolar or/and lingual nerve |
|                 | to symphysis                        | and shape                            | Trismus       |
|                 |                                      |                                      | Hematoma      |
| Coronoid process [32] | No scarring | Requires hospitalization        | Fracture       |
|                 | Easy bone harvesting                |                                      | Trismus       |
|                 | Low morbidity                       |                                      | Hematoma      |
| Incisive fossa [33] | Easy bone harvesting | Type IV bone                        | Tooth injury  |
|                 | Easy bone harvesting                |                                      |               |
|                 | Corticocancellous graft             |                                      |               |
|                 | Presence of osteoprogenitor cells   |                                      |               |
| Mandibular symphysis [34] | Easy bone harvesting | Several post-operative complications | Damaged submental and sublingual arteries |
|                 | Corticocancellous bone, mainly cancellous | Small – medium size defects | Damage to mandibular tooth roots |
|                 | Lower morbidity compared with ramus |                                      | Mental nerve paresthesia – altered lower lip sensation |
| Maxillary tuberosity [35] | Low morbidity | Poor quality and quantity of bone | Alteration of facial contour |
|                 | Easy bone harvesting                |                                      | Oroantral fistula |
|                 | Corticocancellous bone              |                                      | Hematoma      |
|                 | Presence of osteoprogenitor cells   |                                      |               |
| Palate [36]     | Low morbidity                       | Limited bone quantity                | Tooth injury  |
|                 | Easy bone harvesting                |                                      | Nasal floor perforation |
|                 | Corticocancellous bone              |                                      |               |
|                 | Presence of osteoprogenitor cells   |                                      |               |
| Torus [37]      | Easy bone harvesting                | Mainly cortical bone                 | Lingual nerve injury |
|                 | Low morbidity                       |                                      | Vascular injury of the floor of the mouth |
| Zygomatic body [38] | Easy bone harvesting | Limited bone quantity               | Ocular complications |
|                 | Corticocancellous bone              |                                      |               |

* General grafting complications including wound infection, dehiscence, abscess and graft rejection are not mentioned.

that transmission of new unknown pathogens though relatively rare remains valid as they may not be eliminated by existing processing procedures. Also, higher absorption rate and immunogenic response and less revascularization and incorporation compared to autologous grafts has been reported among the disadvantages of this grafting category [43]. Finally, due to the fact that a bone allograft is not a standardised tissue since age, gender and medical status of donors may vary in combination with existing diversity of processing procedures in bone banks, interprets why their properties may differ widely. All processing, maintenance and storage methods must be carefully assessed in terms of disease transmission but also their effect on biological and mechanical properties of the material. For example, although a more vigorous sterilization process can eliminate the chances of disease transmission and infection, it can also reduce osteogenic and
2.1.3. Xenografts

These implants derive from donors of a different species relative to the recipient, usually possess osteoconductive features with limited resorptive potential and are often combined with growth factors or bone grafts of other origin.

Several bone substitutes are included in this category, capable of mass production with a relatively affordable cost. Among their disadvantages is the fact that bone characteristics differ compared to humans while their processing procedure might affect their physico-chemical properties as in the case of allografts as well as possibility of disease transmission and stimulation of immunogenicity [43].

2.1.3.1. Bovine substitutes. Bovine origin bone substitutes were the first xenografts applied to patients, being commercially available in a wide range of products and are considered among the most documented materials of this category. They are characterized by osteoconductive properties, being deproteinized and lyophilized, causing no immune response [14]. However, granules of these materials are considered to be subjected to poor or slow absorption, surrounded by neoplastic bone tissue rather than entering the normal bone remodeling process [44]. Processing at high temperatures to avoid immune reactions, allergies and infectious diseases such as spongiform encephalopathy is considered responsible for modifying the structure of hydroxyapatite which further leads to reduced absorption potential [45,46].

2.1.3.2. Equine substitutes. Equine-derived bone substitutes have been described as having the ability to induce osteoblastic differentiation and angiogenesis while being absorbed by osteoclasts. In addition, the presence of neoplastic bone associated with remodeling effects was observed around the graft material 6 months postoperatively, while being described in cases of successful sinus lift [47,48].

2.1.3.3. Porcine substitutes. Porcine-derived substitutes, recently developed, are considered to exhibit similarities regarding structure and formation compared to human bone, given the similarities of human and porcine genomes. They exhibit osteoconductive characteristics and a low risk of disease transmission [49]. However, reduced absorption capacity of these materials over time and poor development of neovascularization has been described [50]. According to others porcine bone is considered to be equally effective with bovine-derived bone implants [51]. Sinus lift procedures with porcine bone implants have also been performed, exhibiting augmentation capabilities and a high percentage of reabsorption 6 months post-operatively [52].

2.1.3.4. Algae substitutes. Algae bone deratives lack antigenicity and inflammatory host response. This biomaterial has been combined with growth factors like BMPs and TGFβ1 [53,54]. It was documented to exhibit successful sinus augmentation via increase in cancellous bone around biomaterial particles [55]. It is resorbable, gradually substituted by newly formed bone [56].

2.1.3.5. Coral substitutes. Madreporic corals including species Porites, Acropora, Lobophyllia, Goniopora, Polypihlia and Pocillopora have remarkable similarities to cancellous bone. Coral bone grafts have been also applied in jaw defects, presenting osteoconductive properties and functioning as carriers for growth factors, improving bone formation [57]. They exhibit initial poor mechanical strength, effectiveness related to blood supply of recipient cite and fast resorption rate. Several studies have reported the ability to implement this material in dentoalveolar reconstruction with encouraging results [40,58].

2.1.4. Alloplastic materials

The enormous progress in the field of biomaterials science, the risk of infectious diseases transmission and finally, efforts to reduce morbidity and cost has led research into the development of a variety of synthetic origin grafts as alternatives.

Alloplastic bone substitutes cover a wide range of bone replacement or soft tissue support applications, available in many sizes and shapes. Several techniques have been employed including surface texture, mineralized layers formation and the use of bioreactors for cells so that the final product will be able to mimic the environment in which osteoblasts naturally grow. These biomimetic materials characterized by osteoconductive, with no osteoinductive or osteogenic potential on their own, try to act as a three-dimensional scaffold to support cell growth and bone formation, increase cell adhesion and proliferation [59]. Their chemical composition, geometry, microscopic structure and mechanical properties are key factors for successful bone remodeling while in vivo absorption capacity allows for their replacement by neoplastic bone [41].

A heterogeneous group of materials, including calcium phosphate, calcium carbonate, calcium sulfate, bioactive glasses and polymers is represented in this category.

2.1.4.1. Calcium phosphate. These materials have gained special interest due to their composition similarity with natural bone. Hydroxyapatite (HA) and tricalcium phosphate (TCP) are the most important players of this category, further classified into ceramics and cements. The former are subjected to a heat treatment called sintering, further driving to a porous and solid material. Cements are produced in the form of paste, hardening after application within the bone defect site [16].

TCP exhibits good biocompatibility and osteoconductivity, lacking osteogenic or osteoinductive properties [60]. Its’ porous composition permits phagocytosis, absorption, vascularization and bone regeneration. In accordance to other calcium phosphate preparations it has been found to be brittle and weak under tension and shear, but resistant to compressive loads. Compared to HA, TCP is more quickly resorbable and less mechanically stable [61].

HA, representing the main structural inorganic component of bones and teeth has excellent biocompatibility with the human body and can therefore be used as a bone graft. HA crystals possess mainly osteoconductive properties and low resorption rate while they are brittle and fracture prone on shock loading. This bone implant has been established as an excellent carrier of osteoinductive growth factors and osteogenic cell populations [62].

Biphasic calcium phosphate (BCP) results from the mixing of TCP and HA in various concentrations in order to attain desired mechanical properties and absorption rate [63].

2.1.4.2. Calcium sulphate. Calcium sulphate, commonly known as Paris gypsum, was first used as a bone substitute in 1892 for the filling of long bones tubular cavities [60]. It is provided in the form of cement or granules, both products exhibiting biocompatibility, bioactivity, tolerability, carrier material capability, osteoconductivity, easy handling and low cost. Rapid absorption of the material has been noted, faster that new bone formation. Efforts to combine calcium sulphate with other materials, towards the direction of delaying absorption process have been made. Also, this bone implant provides minimal structural support, not indicated in cases where increased mechanical load is expected [64]. In the field of dentistry, it has been extensively applied in periodontal, dentoalveolar and tooth extraction defects [65].
2.1.4.3. Hard tissue replacement (HTR) polymeric substitutes. The most important of the polymers used in bone augmentation is polymethyl methacrylate, a porous biomaterial exhibiting osteo-conductive properties, compressive strength and elasticity similar to cortical bone, but not resorbable. The high temperature which is developed during the polymerization, depending on the exact cement composition may create thermal bone necrosis, damage of blood circulation and membrane formation between bone-cement interface [16].

2.1.4.4. Bioactive glass. Composed of active silicate-based glass, this implant exhibits significantly greater strength compared to calcium phosphates. It is capable of forming a strong bond between the glass and the host bone through hydroxyapatite crystals, a phenomenon called bioactivity. The resorption of bioactive glass is variable, based upon the relative amounts of components like sodium oxide, calcium oxide, silicon dioxide and phosphorous present [66].

3. Conclusion

Over the past decades, extensive research has been accomplished in the field of bone regenerative materials to improve their characteristics such as mechanical strength, molecular composition, bio-compatibility, and degradation capacity in order to resemble features of natural bone. With the passing of time, synthetic implants and other synchronous regenerative methods substitute use of natural bone grafts. The clinician needs to be aware of these substitutes and their properties to achieve the best possible clinical outcome for every patient.

Given that the ideal bone reconstruction material has not yet been acquired, a further effort is required to make this objective feasible. Development of various bone regenerative materials in the form of hybrid ingredient products that include cells, growth factors, and/or gene modifying drugs in combination with the aid of science in biochemistry, engineering and nanotechnology will further open a new horizon in the field of bone regeneration [67].

Acknowledgments and disclosure statements

The authors report no conflicts of interest.

References

[1] Kumar P, Vinitha B, Fathima G. Bone grafts in dentistry. J Pharm Bioallied Sci 2013;5(6):5125–7.
[2] Liu X, Shi B, Zheng Q, Li C. Alveolar bone grafting and cleft lip and palate. plast Reconstr Surg 2017;140(2):359e–60e.
[3] Buser D, Dula K, Hess D, Hirtt HP, Belser UC. Localized ridge augmentation with autografts and barrier membranes. Periodontol 2000;2000(10):151–63.
[4] Malinin TI, Temple HT, Garg AK. Bone allografts in dentistry: A review. Dentistry 2014;4:199. doi:10.4172/2161-1122.1000199.
[5] Bauer TW, Muschler GF. Bone graft materials. An overview of the basic science. Clin Orthop Relat Res 2000;371(February):10–27.
[6] Janicki P. Schmidtmaier G. What should be the characteristics of the ideal bone graft substitute? Combining scaffolds with growth factors and/or stem cells. Injury 2011;42(Suppl. 2):577–81.
[7] Roberts WE, Simmons KE, Garett LP, DeCastro RA. Bone physiology and metabolism in dental implantology: risk factors for osteoporosis and other metabolic bone diseases. Implant Dent 1992;1:11–21. Spring.
[8] Simpson AHRIW, Mills L, Noble B. The role of growth factors and related agents in accelerating fracture healing. J Bone Joint Surg Br 2006;88(6):701–5.
[9] Fernández RF, Bucchi C, Navarro P, Beltrán V, Borie E. Bone grafts utilized in dentistry: an analysis of patients’ preferences. BMC Med Ethics 2015;16(1):71. https://doi.org/10.1186/s12910-015-0044-6.
[10] Bobbert FSL, Zadpoor AA. Effects of bone substitute architecture and surface properties on cell response, angiogenesis, and structure of new bone. J Mater Chem B 2017;5:675–92.
[11] Murphy CM, Haugh MG, O’Brien FJ. The effect of mean pore size on cell attachment, proliferation and migration in collagen glycosaminoglycan scaffolds for tissue engineering. Biomaterials 2010;31(3):461–6.
transforming derived vivo.

Bone grafting and bone regeneration—a review. J Histochem Cytochem 2002;50(2):133–44.

Shibuya N, Jupiter DC. Bone graft substitute: allograft and xenograft. Clin Podiatr Med Surg 2015;32(January (1)):21–34.

Tovar N, Jimbo R, Gangolini R, Perez I, Manne L, Yoo D, et al. Evaluation of bone response to various anorganic bovine bone xenografts: an experimental calvaria defect study. Int J Oral Maxillofac Surg 2014;43(February (2)):251–60.

Cypher TJ, Grossman JP. Biological principles of bone graft healing. J Foot Ankle Surg 1996;35(September–October (5)):413–7.

Jensen SS, Broggini N, Hjorting-Hansen E, Schenk R, Buser D. Bone healing and graft resorption of autograft, anorganic bovine bone and beta-tricalcium phosphate. A histologic and histomorphometric study in the mandibles of minipigs. Clin Oral Implants Res 2006;17(June (3)):237–43.

Tauro JC, Parsons JR, Ricci J, Alexander H. Comparison of bovine collagen xenografts to autografts in the rabbit. Clin Orthop Relat Res 1991;266(May):271–84.

McDuffee LA, Anderson GL. In vitro comparison of equine cancellous bone graft donor sites and tibial periosteum as sources of viable osteoprogenitors. Vet Surg 2003;32(September–October (5)):455–63.

Rivara F, Negri M, Lunetti S, Parisi L, Toffoli A, Calcisoli E, et al. Maxillary sinus floor augmentation using an equine-derived graft material: preliminary results in 17 patients. Biomed Res Int 2017;2017, http://dx.doi.org/10.1155/2017/9164156, 9164156.

Salamanca E, Lee WP, Lin CY, Huang HM, Lin CT, Feng SW, et al. A novel porcine graft for regeneration of bone defects. Materials 2015;8(5):2523–36.

Salamanca E, Hsu C-C, Huang H-M, Teng N-C, Lin C-T, Pan Y-H, et al. Bone regeneration using a porcine bone substitute collagen composite in vitro and in vivo. Sci Rep 2018;8(January (1)):584, http://dx.doi.org/10.1038/s41598-018-19629-y.

Lee JH, Yi GS, Lee JW, Kim DJ. Physicochemical characterization of porcine bone-derived grafting material and comparison with bovine xenografts for dental applications. J Periodontal Implant Sci 2017;47(Decembers (6)):388–401.

Barone A, Ricci M, Covani U, Namnikul U, Azamehr I, Calvo-Guirado JL. Maxillary sinus augmentation using prehydrated corticocancellous porcine bone: histomorphometric evaluation after 6 months. Clin Implant Dent Relat Res 2012;14(June (3)):373–8.

Turchi E, Cvikl M, Watzinger E, Weißenböck M, Yerit K, Thurnher D, et al. In vitro growth and differentiation of osteoblast-like cells on hydroxyapatite ceramic granule calcified from red algae. J Oral Maxillofac Surg 2005;63(June (6)):793–8.

Gille J, Dorn B, Kekov J, Bruns J, Behrens P. Bone substitutes as carriers for transforming growth factor-β1 (TGF-β1). Int Orthop 2002;26(4):203–6.

Christian S, Doris M, Alexis S, Georgios L, Else S, Franz K, et al. The fluorohydroxyapatite (FHA) FRIOS® Algipore® is a suitable biomaterial for the reconstruction of severely atrophic human maxillae. Clin Oral Implants Res 2003;14:743–9.

Scarano A, Degidi M, Perrotti V, Piattelli A, LIegji G. Sinus augmentation with phycogene hydroxyapatite: histological and histomorphometrical results after 6 months in humans. A case series. Oral Maxillofac Surg 2012;16(March (1)):41–5.

Demers C, Hamdy CR, Corsi K, Chellat F, Tabrizian M, Yahia L. Natural coral exoskeleton as a bone graft substitute: a review. Biomed Eng 2002;12(1):15–35.

Scarano A, Degidi M, LIegji G, Pecora G, Piattelli M, Orsini G, et al. Maxillary sinus augmentation with different biomaterials: a comparative histologic and histomorphometric study in man. Implant Dent 2006;15(June (2)):197–207.

Al’Ghamdi AS, Shibly O, Ciancio SG. Osseous grafting part II: xenografts and alloplasts for periodontal regeneration—a literature review. J Int Acad Periodontol 2010;12(April (2)):39–44.

Pecora G, Andreana S, Margarone JE, Covani U, Sottosanti JS. Bone regeneration with a calcium sulfate barrier. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;84(October (4)):424–9.

Yu X, Tang X, Gohil SV, Laurencin CT, Raymond T. Biomaterials for bone regenerative engineering. Adv Healthc Mater Adv Healthc Mater 2016;5(June (9)):1268–85.

Meffert RM, Thomas JR, Hamilton KM, Brownstein CN. Hydroxyapatite as an alloplastic graft in the treatment of human periodontal osseous defects. J Periodontol 1985;56(February (2)):63–73.

Daculsi G, LeGeros R, Nery E, Lynch K, Kerebel B. Transformation of biphasic calcium phosphate ceramics in vivo: ultrastructural and physicochemical characterization. J Biomed Mater Res 1989;23:883–94.

Pfröringer D, Harrasser N, Mühlhofer H, Kiokekli M, Stemberger A, Griensven van M, et al. Osteoinduction and -conduction through absorbable bone substitute materials based on calcium sulfate: in vivo biological behavior in a rabbit model. J Mater Sci Mater Med 2018;29(2):17, http://dx.doi.org/10.1007/s10856-017-6017-1.

Crespi R, Capparé P, Cherlone E. Magnesium-enriched hydroxyapatite compared to calcium sulfate in the healing of human extraction sockets: Radiographic and histomorphometric evaluation at 3 months. J Periodontol 2009;80(February (2)):210–8.

Giannoudis PV, Dinopoulos H, Tsiridis E. Bone substitutes: an update. Injury 2005;36(November (Suppl. 3)):S20–7.

Zhang L, Webster TJ. Nanotechnology and nanomaterials: promises for improved tissue regeneration. Nano Today 2009;4(February (1)):66–80, http://dx.doi.org/10.1016/j.nantod.2008.10.014.