2 New Developments and Biomaterials in Reconstruction of Defects of the Alveolar Ridge in Implant Surgery: Part 1—Biomaterials

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2.1 Introduction: Bone Biology and Healing Process

Bone is a tissue that has the ability of self-regeneration leading this healing process in most of the cases to a fully morphologic and functional regeneration.

The knowledge of bone biology is essential to understand the required conditions for a successful reconstruction. The more evident function of the bone skeleton is to allow the locomotion and protection of internal organs, but the bone is also the siege of the hematopoiesis and an essential component in the homeostasis of the phosphor-calcic equilibrium of the organism. Thus, the bone is in a perpetual renewal cycle through resorption and regeneration, allowing the ionic release and capture and response to biomechanical demands [1, 2]. Although the main components of the bone remain homogeneous, including an inorganic mineralized matrix of apatites associated to a protein matrix mainly composed of type 1 collagen, the bone can present different architectural and biological properties, showing the cortical bone a compact structure while the trabecular bone has spongy structure.

In order to understand the prerequisites for a successful bone reconstruction, it is also interesting to know the bone healing process. A bone injury is firstly leading to the formation of an hematoma associated to an inflammatory response and the recruitment of signaling molecules (BMPs, ILs, VEGFs, FGFs,…) involved in bone homeostasis. Thereafter, the process continues by the formation of a callus undergoing chondrogenesis and progressive calcification. Finally, the blood vessels growth into the callus carries both chondroclasts, which resorb the calcified cartilage, and osteoprogenitor cells initiating the bone formation process. It is also important to notice that to complete the bone healing process the stability of the callus is essential, otherwise, the cartilaginous callus is not replaced and results in pseudarthrosis. Thus, bone has strong regenerative capacities, nevertheless, in case of large defects or pathological local condition (infection, insufficient vascularization, instability of the

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callus,…) the healing process can be compromised which can have an impact in graft's success. In these cases, four elements are essential in the bone graft's healing process and shall be taken in account in every bone grafting procedure: presence of osteogenic cells, osteoconductive scaffold, mechanical environment, and growth factors [3]. Furthermore, a fifth element can't be ignored, the vascularization of the graft and its surrounding tissues.

2.2 Bone Grafts

A bone graft can be defined as an implanted material that promotes osteogenesis through osteoconduction, osteoinduction, and osseointegration. The osteogenesis is the property to produce new bone, whereas osteoconduction is the capability of a grafted material to allow bone growth on its surface or down into pores. Osteoinduction is the capability to recruit and stimulate differentiation of immature cells into bone forming cells and osseointegration is the ability to bind the graft to the surrounding bone without interposition of fibrous tissue [4–7]. All bone grafts or substitute materials can be compared through these characteristics.

The bone grafting procedure is a very common procedure with up to 2.2 million performed worldwide each year while the bone is the second most transplanted tissue after blood. The cost of these procedures is estimated around $2.5 billion per year [8, 9] being the craniofacial field one of the most popular indications for bone grafting [10]. The concept of **autologous graft** means that the tissue is collected of and grafted on the same patient. Due to its biological properties, the autologous bone graft remains the gold standard in bone reconstruction for decades.

The grafted bone brings to the reconstructed site cells, matrix and molecules, guiding and improving the bone healing process. Depending on the type of bone, two type of grafts can be considered concerning its structural features, the cancellous and the cortical bone. The cancellous bone shows high porosity having strong osteogenic properties whereas, on the other hand, the cortical bone has higher density and thus better mechanical properties. The cancellous bone is frequently used to fill limited defects with low mechanical strength while the cortical bone is frequently used as an onlay graft in order to increase the alveolar ridge. It is exposed to a lower vascularization and mechanical constraints of the surrounding mucosa. Indeed during the healing process, mucosa induces an increase of the pressure on the underlying grafted bone and so a higher resorption rate. In fact, many factors are involved in the resorption process but it seems clear that the cortical bone graft has a higher resorption rate. The autograft can be harvested from different sites (Fig. 2.1); however, despite its biological and mechanical properties, the autograft presents a major disadvantage which is the morbidity of the donor sites [11–13], with possible impact on patient quality of life. Moreover, the potential amount of bone that can be harvested is limited especially in case of pediatric or geriatric patient. That is why alternatives as allografts and xenografts have been considered.

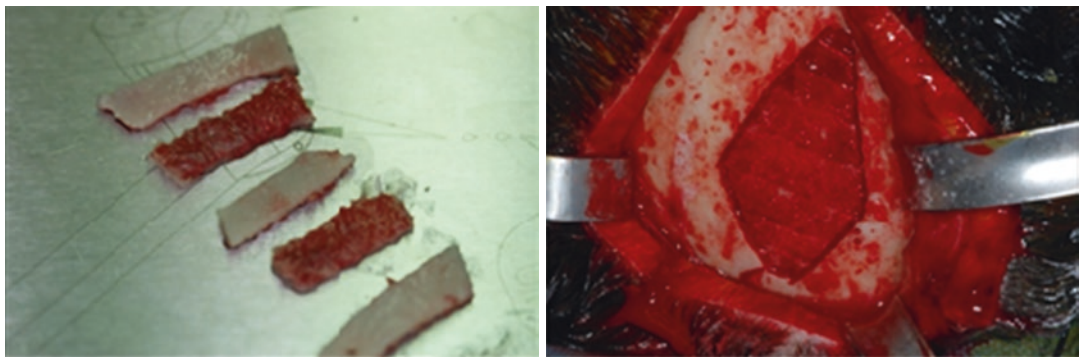

Fig. 2.1 Calvarial bone sample for bone graft

Allografts are tissue harvested from one individual and transplanted to another individual of the same species with a different genotype, whereas **xenografts** are harvested from other species. They both eliminate the donor site morbidity and are available in large quantity having also osteoconductive and osteoinductive properties but in comparison with the autologous grafts, allografts and xenografts present a lower osteogenic potential, increase the rejection risk due to the immune response and present a risk of disease transmission. Furthermore, the procedure required to decrease the risk of disease transmission also negatively impact in their biological and mechanical properties. Today, allografts are rarely used for implant surgery in comparison with the popularity of xenografts in this field due to their easy access for practitioners.

Thus, due to the multiple problems related to the use of bone grafts, research is carried out in order to find an ideal bone substitute which should present the biological properties of the autograft combined with unlimited amount and limited cost. In order to reach that goal, different approaches are possible including tissue engineering [14, 15]. Tissue engineering is based on the use of cells, molecules, and matrix that can be used independently or combined aiming to maintain, reestablish, or improve tissue architecture and function. Considering the specific Bone Tissue Engineering (BTE) field, some key points have to be taken into account: a scaffold shall mimic the bone extracellular matrix with osteoinductive properties facilitating osteogenic cell adhesion, it shall differentiate the cells to the desirable phenotype through osteoinductives properties and allow sufficient vascularization and nutrition of the construct to complete the healing process [14].

2.3 Biomaterials and Scaffolds

Scaffolds are to date the most important issue in bone tissue engineering. Scaffolds are materials designed to support and facilitate the bone healing process by allowing the undifferentiated cells migration and specialization, sequestration of extracellular matrix components, vascularization development, and three-dimensional tissue organization. They also shall provide structural stability to the reconstructed site, withstanding mechanical strength supported by the bone. Biomaterials are materials of natural or synthetic origin suitable to be implanted and interact with living tissue.

Scaffolds can be divided in organic and inorganic, with biological or synthetic origin. The advantages of biological scaffolds are that they have better biocompatibility, bioresorption ability, and regenerative properties (osteoconduction, osteoinduction, osteogenesis, and osseointegration) in comparison with synthetic materials although they also can present immune response. The immune reaction and mechanical failures are the two main causes of failure in bone reconstruction protocols.

2.3.1 Natural-Origin Biomaterials

Collagens are one of the most widely present proteins in the human body and provide stability and strength to many tissues from skin till bones [16]. Type I collagen is the main component of the extracellular matrix of the bone and is one of the most popular organic biological material for bone tissue engineering. Integration of collagen on the surface of scaffolds improves cellular proliferation and osteoblastic differentiation. Collagens can also be used as carriers for other molecules as bone morphogenetics proteins, enhancing the new bone formation [17]. However, collagens present poor mechanical properties as a major limitation for bone tissue engineering which can be improved combining them with other materials with better mechanical features.

Chitosan is another example of organic biological material which can be used for bone tissue engineering. It's a linear polysaccharide with bending ability but poor mechanical properties. Chitosan modifies its structure depending on the acid-base environment. Thus, in a neutral environment, chitosan maintains its structure but solubilizes and degrades in an acidic medium. Chitosan can be used as a carrier in polymeric

nanoparticles and is used in combination with other materials for bone tissue engineering [18, 19]. However, the resorption of the polymer can lead to aseptic inflammation which negatively affects the bone healing process.

Summarizing, even if they are used for implant procedures, the major limitations in the use of natural-origin biomaterials are the difficulties in refining them, their potential immunogenicity and the poor mechanical properties in comparison to the bone. Thus they shall be considered as an alternative when bone grafts are not possible.

2.3.2 Synthetic Biomaterials

In order to reduce the problems related to the use of natural-origin biomaterials, a challenging field has been the development of polymeric synthetic biomaterials [20–22] like polyglycolic acid (PGA), polylactic acid (PLA), or polylactic-*co*-glycolic acid (PLGA) that are very promising in bone tissue engineering field but are not today included in practitioners' current practice.

The synthetic bone substitutes share several advantages over allografts, including unlimited supply, easy sterilization and storage but their biocompatibility, biodegradability, and regenerative properties are lower than those of natural scaffolds [15]. Since the initiation of bone tissue engineering procedures more than three decades ago, different options have been considered but calcium phosphate matrix (hydroxyapatite, beta-tricalcium phosphate) and bioactive glasses remain as the most used currently because of their morphological and biological similarities to the inorganic part of bone [23]. In fact, bone is a composite material composed of both mineral (calcium phosphate) and protein matrix. The proteins provide its flexibility to the bone while calcium phosphate gives its compressive strength, although linked to their low plasticity, the calcium phosphate matrix (CaP) can be also fragile.

Biological apatites (BA) are the mineral phase of bone. They have a very flexible composition linked to their ability to chemical substitution. In fact, other components such as Mg, Na, Si, Cl, K, CO_3 and F can be included in their structure, leading to variations in their chemical and mechanical properties [24]. On the other hand, synthetic apatites like synthetic hydroxyapatite (S-HA) have a stable composition and do not include "impurities." Moreover, crystals of S-HA are much bigger than the BA [25]. This induces variations in their biological and mechanical properties in comparison to the BA and even if they are considered to be biocompatible, osteoconductive bioactive and have a great affinity for growth factors and proteins, they have a lower solubility and low osteoinductive potential. Furthermore, a lot of parameters also influence the biological and physical properties of the S-HA scaffolds, like sinterization temperature and pore size (micro- and macroporosity). In order to simplify, we may say that for synthetic phosphocalcic matrix, the microporosity and resorption potential vary inversely with the increase of the sintering temperature and the increase of mechanical resistance [26–28] .

The beta-tricalcium phosphate (β-TCP) is another synthetic calcium phosphate that presents a less stable crystalline phase than S-HA and thus a higher degradation rate and better osteoinductive property. Moreover, its mechanical properties like compression and tensile strength are very similar to that of cancellous bone, which make β-TCP one of the most popular options for bone tissue engineering. The most recent and promising approach to date in phosphocalcic matrix is the development of biphasic calcium phosphates (BCP) to combine the properties of both materials, hydroxyapatite and tricalcium phosphate. Two different approaches are possible to produce that BCP. The most popular and the easier is to mix HA and β-TCP powder and modify their ratio to modulate their mechanical and physiological properties. However, the inhomogeneity of the proportions of these two phases in the material may lead to variation of the mechanical and biological properties inside the matrix. The second approach consist in a molecular mix of HA and β-TCP during the synthesis process which is supposed to guaranty a higher homogeneity of the material and its physicochemical properties [29, 30].

Multiple studies on S-HA, beta-tricalcium phosphate (β-TCP), and bicalcium phosphate (BCP) have shown that a fast resorption is beneficial concerning osteoinduction properties; however, a stability of the surface is necessary for bone formation. By modulating S-HA/β-TCP proportions in the BCP, it is possible to modulate their resorption rate and mechanical properties and thus to mimic the properties of the repaired bone defect [31]. A high proportion of β-TCP has been demonstrated to be better to develop early bone formation [32]. Like other calcium phosphate (CaP) matrix, the porosity and architecture of the BCP matrix also play a major role in their properties [33, 34]. Thus, to reproduce the biological properties of the bone, an adequate architecture is essential. In fact, it has been well documented that the pore size plays a major role in neoangiogenesis, osteoconduction, and new bone formation [35, 36]. Today, apatite materials are frequently used in implants surgery to fill bone defect. They can be used alone or in association with bone graft depending on the procedures.

2.4 The Impact of the New Technologies on CaP Matrix

The computer assisted design (CAD) associated with addictive technologies known as 3D printing is probably a "game changer" in the conception of our matrix. In fact, CAD procedure allows to anticipate the control of both macro and micro architectures of the matrix (Fig. 2.2a, b), virtually reproducing the architectural characteristics of trabecular and cortical bones (Fig. 2.3). In a near future, bone defects could be repaired through the accurate reproduction of the previous architecture in order to simplify and to increase the precision of the reconstruction procedures (Figs. 2.4 and 2.5).

Different printing techniques are possible to create a calcium phosphate matrix. The most promising to date seems to be the stereolithography,

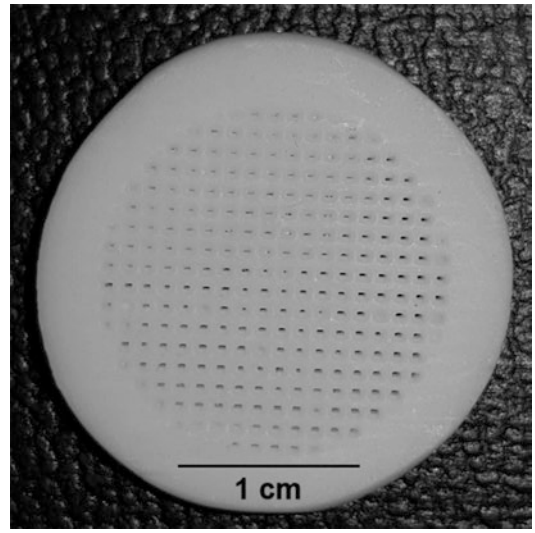

Fig. 2.3 Hydroxyapatite architecture of trabecular (macroporous) and cortical (dense) bones printed by ceramic stereolithography

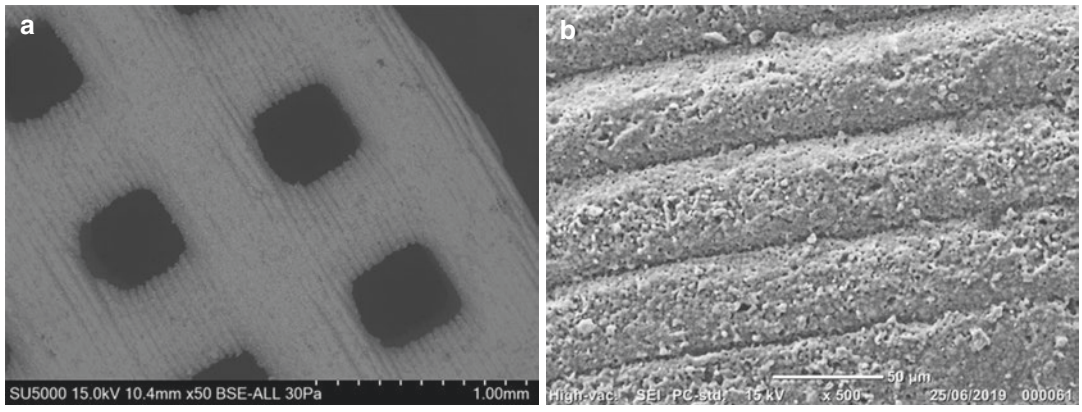

Fig. 2.2 (**a**) SEM morphology of BCP macroporous structure produced by ceramic stereolithography. (**b**) SEM morphology of β-TCP microporous structure produced layer by layer by ceramic stereolithography

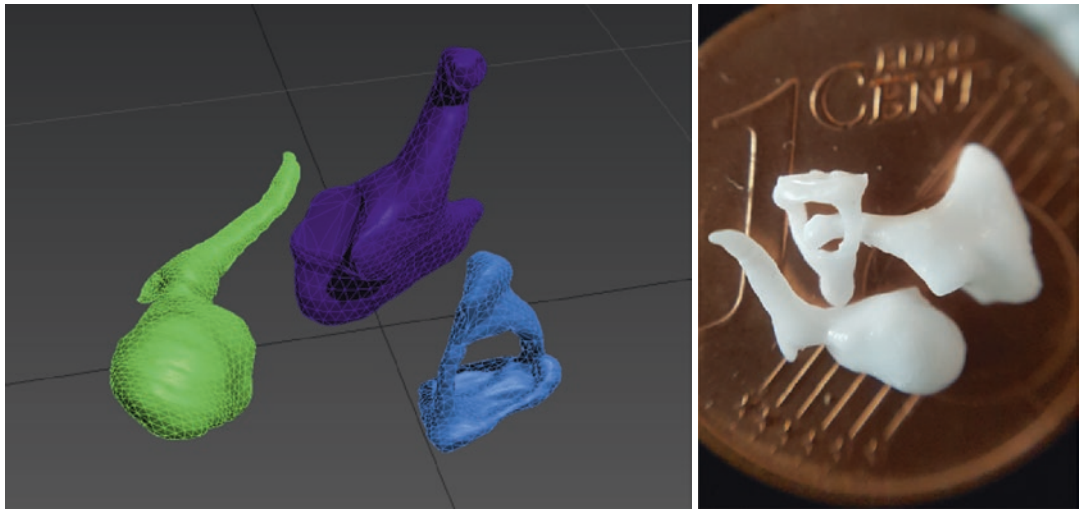

Fig. 2.4 The smallest bones in the human body (of the middle ear) produced by stereolithography with a resolution of less than 50 μm of dense hydroxyapatite

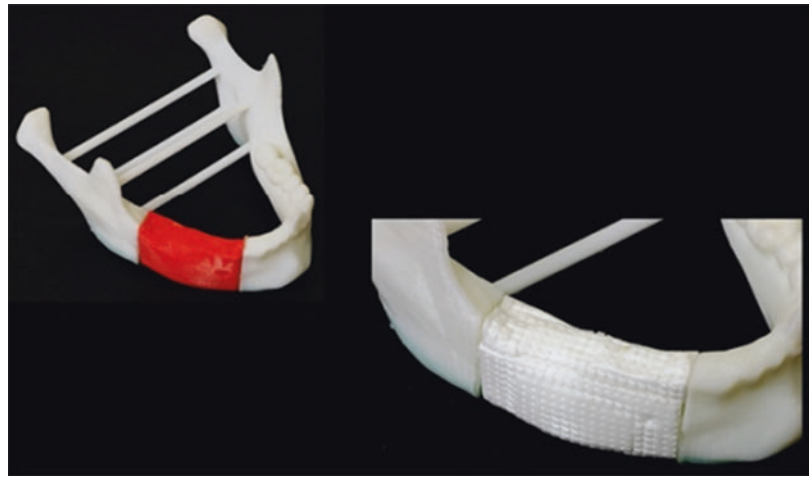

Fig. 2.5 Demonstration of a bone defect reconstructed with printed phosphocalcic matrix

consisting in the polymerization layer by layer of a photo-curable resin mixed with phosphocalcic particles. After the end of the printing process, matrix has to be sintered in order to finish the shaping process (Fig. 2.6). Main advantage of this technique is its high resolution (under 100 μm) but it involves potential contamination of the product from resin. The laser casting technique uses a high resolution laser to produce a selective layer by layer thermal binding of the particles. Like the stereolithography, the main advantage of that technique is its resolution but remains expensive to date. Finally, the third and most popular technique is the material extrusion 3D printing. It consists in a continuous material deposit through an extruder. The layer by layer deposit finally results in a 3D structure that need to be sintered to complete the shaping process. The limit of the extrusion technique is its lower resolution compared to stereolithography and laser casting [37, 38].

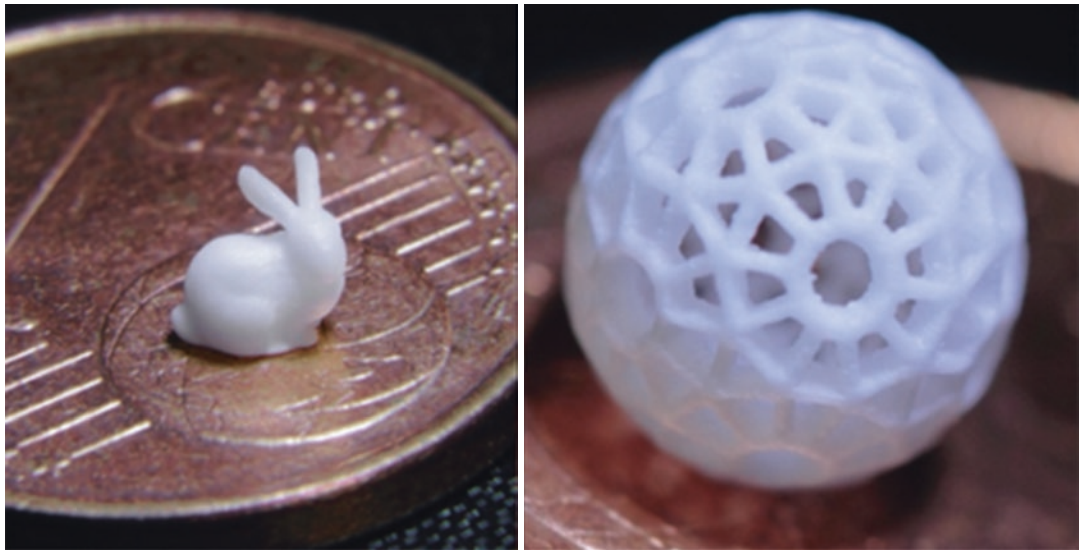

Fig. 2.6 Examples of phosphocalcic matrices printed using stereolithography. Note the high resolution of the produced pieces and the complex design achieved

2.5 Conclusion

To date, the autologous bone graft shall remain the gold standard in the treatment of bone defects in implant surgery. However, the needs in terms of bone regeneration are constantly increasing and the autologous graft can't be the only answer. Allografts and xenografts are useful but not ideal alternatives as they present a risk of disease transmission and rejection, that's why the development of synthetic grafting material has been introduced.

Tissue engineering including CaP matrix associated with 3D printing techniques seem to be promising for the next future. However, these techniques should certainly combine composite materials and introduce a cellular and molecular approach in order to mimic the bone structure and function to become the new gold standard in bone reconstruction.

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