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Chapter 3

Composite Calcium Phosphate/Titania Scaffolds in Bone Tissue Engineering

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Additional information is available at the end of the chapter

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Abstract

Titanium and its alloys have been extensively used as implantation materials due to their favorable properties such as lower modulus, good tensile strength, excellent biocompatibility, and enhanced corrosion resistance. However, their intrinsic bioinertness generally prevents a direct bond with the bone on the surface especially at an early stage of implantation. In recent years, bioactive scaffolds for bone regeneration are progressively replacing bioinert prostheses in orthopedic, maxillofacial, and neurosurgery fields. Given the need of enhanced mechanical strength, several combinations of bioactive and reinforcing phases have been studied, but still no convincing solutions have been found so far. In this context, titanium oxides are light and high-resistance bioactive materials widely employed in dental and bone application due to their capacity of forming strong bonds with bone tissue via the formation of a tightly bound apatite layer on their surface. The addition of titania particles to hydroxyapatite has attracted considerable attention based on the assumption that resulting materials can enhance osteoblast adhesion and promote cell growth while also providing high strength and fracture toughness in the final composite material, thus being adequate for load-bearing applications.

Keywords: hydroxyapatite, titania, bioactive composites, porous scaffolds, mechanical strength, load bearing

1. Introduction

The regeneration of critical-size bone defects, particularly in load-bearing site, still represents a remarkable challenge in orthopedics. Indeed, these clinical cases require the use of scaffolds with cell-instructive ability and remarkable strength to cope with the early and complex

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biomechanical stimuli in vivo [1]. As the use of autografts or allografts suffers many restrictions and drawbacks, particularly in the case of large defects, synthetic biomaterials are today considered as elective in this respect; however, there is still a lack of suitable materials associating bioactivity and high strength. Natural bone is a hybrid nanocomposite capable of outstanding mechanical performance and ability to establish an active dialogue with cells. In particular, the bone is composed of an inorganic compound (60%), a nearly amorphous calcium phosphate with the crystal structure of hydroxyapatite (HA), heterogeneously nucleated on an organic component prevalently made of type I collagen. The collagen phase provides the bone with great flexural strength, while the mineral component increases the bone compression strength.

The unique factors that contribute to the toughness of bone are the presence of nano-size apatite crystals and a dense network of collagen fibers.

For that reason, in the last decades, the research on biomaterials and scaffolds able to favor bone tissue regeneration upon implantation, while also mechanically supporting the anatomic site affected by lack of bone, has been increasing. In this respect elective materials are calcium phosphates, due to their high chemical similarity with the bone mineral. However, they suffer of low mechanical strength that makes them not suitable to be implanted in load-bearing site. Therefore, a new approach was focused on the development of ceramic composites associating high bioactivity and strength.

The present chapter will provide an overview to illustrate novel potential approaches to develop reinforced bioactive scaffolds to assist the regeneration of load-bearing bony sites, considering that serious drawbacks can arise in case of mechanical mismatching at the bone/biomaterial interface. In particular, the chapter will highlight the use of titanium dioxide, which is a well-established biomaterial for bone applications, as a promising nanomaterial with the ability to reinforce calcium phosphate matrixes.

2. The need of mechanically competent bioactive implants for bone regeneration

In most of load-bearing applications, the main target is the achievement of high mechanical strength. However, this approach can limit the success of the implant when it comes to obtain substantial bone regeneration. As a matter of fact, to date bioinert metallic prostheses are implanted upon occurrence of bone impairments or fractures. These devices are for sure mechanically competent in restoring the bone shape and eventually the biomechanical function of joints in relatively short timing [2]. However, their well-known great mechanical performance may be also detrimental, particularly in the long term. In fact, current implants utilized in orthopedic and maxillofacial surgeries suffer various clinical drawbacks, such as implant loosening, wear, and limited compatibility with the bone in permanent metal implants [3]. In this condition, the excessive stiffness exhibited by metallic implants, generally much greater if compared with the elastic behavior of the bone, results in improper prosthesis-to-bone load transfer and stress shielding that can impair the stability of the implant and its long-term performance (**Figure 1**) [4].

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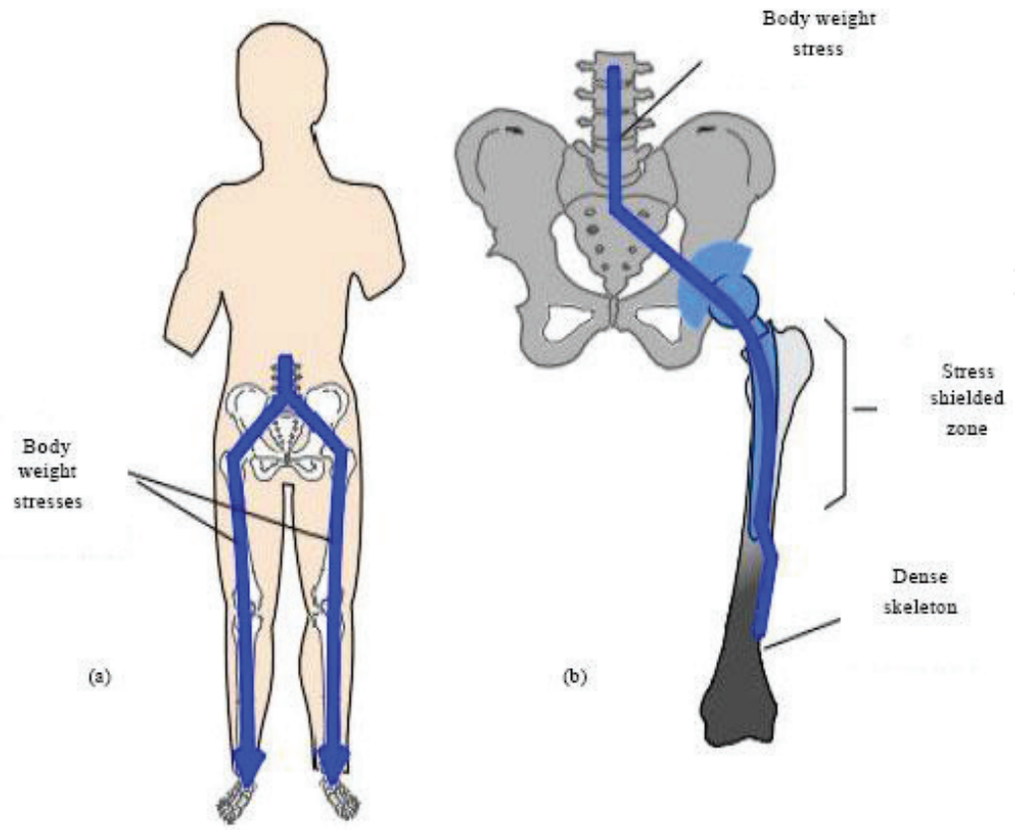


Figure 1. Simple scheme of stress shielding [5].

Briefly, as a simple mechanical rule, considering every composite system composed of two materials where one component is stiffer, the stiffer component will sustain the greater part of the load. In the normal healthy skeleton, the stresses flow symmetrically from there downward through both hip joints, thighbones, knee joints, lower leg bones, and feet onto the floor (**Figure 1a**).

In case of total hip joint replacement, the shaft component generally takes over the majority of the stresses; in this case, the body weight primarily flows down from the joint center and then through the shaft of the device. As a consequence, the upper part of the thighbone is unloaded, thus resulting in weaker areas more susceptible to fracture. Moreover, the skeleton around the tip of the femoral component is overloaded, resulting in a thicker and stronger part. The shaft component of a total hip device is much stiffer than the skeleton and will take the greater part of the body weight load. Consequently, the shaft component is overloaded, whereas the skeleton around the shaft is unloaded (**Figure 1b**) [5].

Unfortunately, the thickening of the skeleton is, in most cases, painful. The patients with cementless shafts of total hip devices often claim about the pain in the thigh, especially during the first years after the surgery [6].

In turn, this can provoke localized osteoporosis and bone resorption, loosening, and detachment of the prosthetic device [7], thus impacting on the course of patient rehabilitation and on the need of repeated revision/correction surgery.

Commonly observed complications after prosthesis removal are infections, impaired wound healing, secondary fractures, tissue and nerve damage, and postoperative bleeding. There is some evidence indicating that the postoperative complication rate depends on the specific localization of the implanted material [8].

Indeed, the above reported drawbacks mostly occur as the used bone/implant systems are often integrated only at the surface [1].

In this respect, bone implants should exhibit substantial cell-instructive ability in order to trigger and sustain the cascade of cell-based phenomena at the basis of new bone formation and organization [9]. Key phenomena in this respect are protein adhesion including the formation of bonds between cell surface receptors (integrins) and the protein functional groups (ligands) (**Figure 2**) [10]. Then, cytoskeletal reorganization with progressive cell spreading on the substrate can take place. Upon implantation in vivo, there are several factors affecting how the proteins will adhere to the material, for example, surface chemistry, surface energy/tension/wettability, roughness, crystallinity, surface charge, and mechanical properties. After this first-stage extensive implant, colonization should take place, driven by a diffuse porosity enabling cell penetration and new bone formation into the inner part of the implant. In this respect, the implant nanotopography can influence the attachment and function of bone cells by modulating key signaling effects essential for their survival [11].

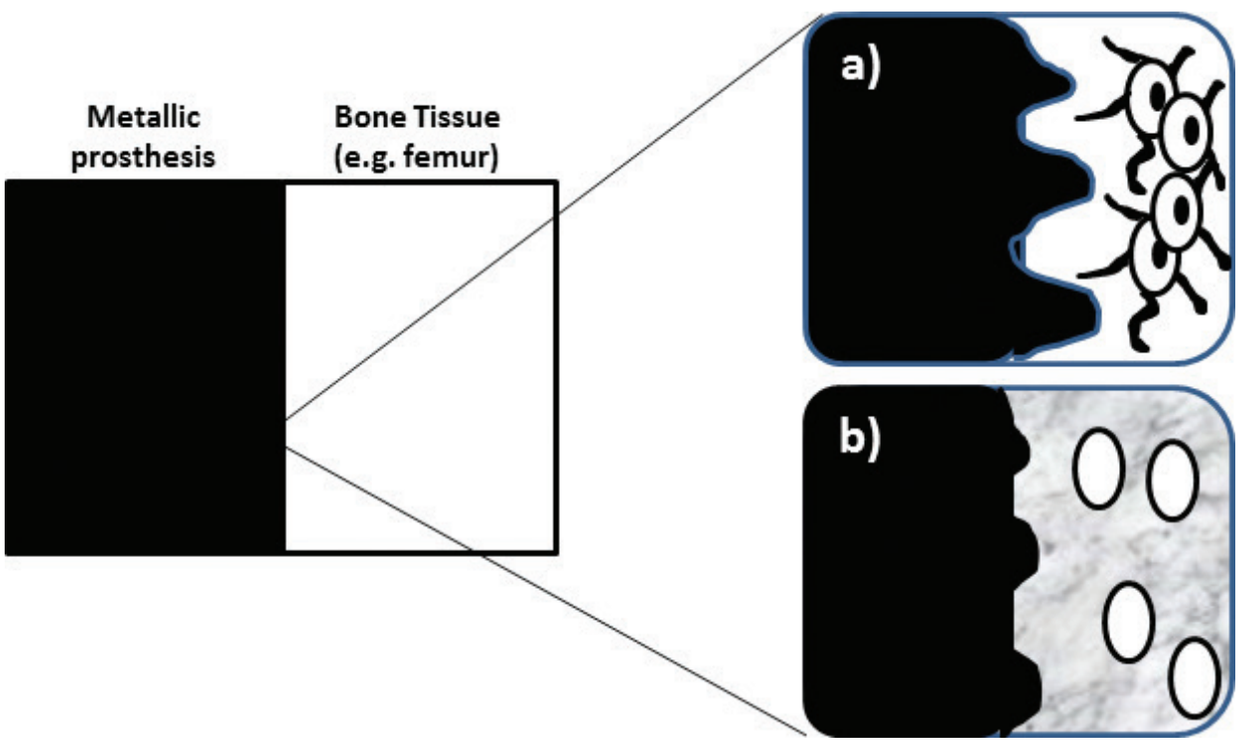


Figure 2. Graphical overview of the effect of surface microstructure on the interaction between a metallic prosthesis and bone tissue: (a) osseointegration, the surface features are able to induce bone formation, leading to long-lasting interaction without side effects; (b) short-loss implant, the surface is now detrimental for bone tissue regeneration, leading to dead bone cells.

Nowadays, it is widely accepted that substantial mimesis of the physicochemical, morphological, and mechanical features of the bone are crucial requisites for regenerative bone scaffolds, particularly in case of repair of long and load-bearing bone segments [12–14]. Indeed, such features can properly drive physiological processes of bone regeneration, to obtain the full recovery of the diseased tissue with all its function. In this respect, recent progresses in materials science research developed a variety of bioactive scaffolds for the healing and repair of damaged or missing bone parts, which are progressively replacing bioinert implants in an increasing number of applications in orthopedic, maxillofacial, and neurosurgery fields [9].

Biomaterials based on hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$) or β-tricalcium phosphate (TCP: β-$Ca_3(PO_4)_2$) have attracted considerable interest for orthopedic and dental applications, thanks to their noticeable chemical resemblance to the mineral component of the bone which provides intrinsic biocompatibility and osteointegration ability [15, 16].

Particularly, tricalcium phosphate has been used in clinics to repair bone defects for many years [17, 18]. As well, a wide range of bioactive materials has been investigated so far, in alternative to calcium phosphates, including bioglasses and apatite-wollastonite glass-ceramics [19–21]. The main attractive feature of such bioceramics is their ability to form a direct bond with the host bone resulting in a strong interface compared to bioinert or biotolerant materials that form a fibrous interface [22]. For biomedical applications the incorporation of biomimetic foreign ions in the HA structure (CO_3^{2-}, Mg^{2+}, SiO_4^{4-}) is needed to increase its functionality in terms of stimulation of the natural bone regeneration processes [23].

However, applications of these materials for long bone replacement are hindered by their insufficient strength and toughness [24].

Also, some calcium phosphates can suffer a relatively high dissolution rate in simulated body fluid that affects their long-term stability [25]. In this context, a great deal of research effort has been devoted so far to develop methods of processing hydroxyapatite with good mechanical properties and high resistance to corrosion [26]. As a general rule, ceramic oxides or metallic dispersions have been introduced as reinforcing agents [27, 28]. In respect to the use of reinforcing ceramics, several attempts have been performed by the addition of aluminum or zirconium oxide to calcium phosphate matrices [29, 30]. The main problems arising when developing such materials mainly concern phase decomposition as a consequence of the chemical interactions between HA and the reinforcing phases at high temperatures. In fact, ceramic materials have to be subjected to sintering process for physical consolidation; in the case of ceramic composites, the phenomena of grain coalescence induced by the thermal treatment can thus coexist with solid-state reactions between the ceramic components which often gives rise to formation of undesired phases and phase decomposition. In this context, HA largely decomposes into tricalcium phosphate, and although in many cases the presence of zirconia improves the mechanical resistance of the final composite, secondary phases depressed the bioactivity and bioresorbability of the scaffolds. In various cases, the formation of secondary phases also resulted into volume modifications in the ceramic body, thus possibly inducing microcracks in the final scaffold after the sintering treatments [31, 32].

Among the most interesting ceramics for composite scaffolds, bioactive calcium silicates were also explored as biomaterials for hard tissue repair and replacement since the early 1970s,

when Hench and coworkers invented Bioglass®, a silico-phosphate-based glass with composition close to that of bone mineral [20]. However, due to their nature, bioactive glasses were not indicated for scaffold reinforcement; however, the presence of silicon in bone scaffolds has always been addressed as promoter of new bone formation in vivo, due to its ability to be a center for nucleation of apatite phase in physiological environment [33]. On this basis, calcium silicate phases such as dicalcium and tricalcium silicate, as well as wollastonite or pseudo-wollastonite ($CaSiO_3$), were widely investigated as scaffolds or cements [34, 35]. In particular, the development of composites made of HA reinforced with dicalcium silicate was investigated [36], on the basis of its high flexure strength (≈200 MPa) and reduced elastic modulus (≈40 GPa) [37], compared with HA, thus resulting as promising compositions for bone scaffolding. As a main drawback, calcium silicates exist in a variety of polymorphs stable in different conditions of temperature [38], thus making difficult to obtain pure phases and avoid decomposition detrimental for the mechanical properties.

A different system that recently attracted the interest of scientists is given by titanium (Ti) and its alloys, particularly titanium dioxide (TiO_2), which have been already validated and extensively used as implantation materials due to their favorable properties such as lower modulus, good tensile strength, excellent biocompatibility, and enhanced corrosion resistance [39].

3. Strengths of titanium dioxide in bone tissue engineering

Titanium oxide has been extensively investigated as a biomaterial due to its excellent biocompatibility and superior corrosion/erosion resistance, as well as high stability [40]. The addition of titania particulates to HA has attracted considerable attention based on the assumption that titania is capable of enhancing osteoblast adhesion and inducing cell growth [41].

Titanium oxides (anatase and rutile) are light and high-resistance bioactive materials widely employed in dental and bone application due to their capacity of forming strong bonds with bone tissue via the formation of a tightly bound apatite layer on their surface [33, 42–44].

In particular, rutile is a very interesting biomaterial for developing bioactive ceramic composites with improved mechanical performances [45].

In this respect, in spite of the numerous studies and applications of HA/TiO_2 composites as bioactive coatings for load-bearing titanium prostheses [46–49], only a few studies were reported so far about the development of bulk TiO_2-containing composites addressed to the development of bone scaffolds [50, 51].

The use of spark plasma sintering and hot pressing to obtain TCP/TiO_2 composites from hydroxyapatite and titania nanopowders has been previously reported [51, 52], whereas Nath et al. used metallic titanium by traditional sintering at different maximum temperatures [50]. In these works, an accurate physicochemical description of the phenomena occurring after thermal treatment of HA/TiO_2 mixtures pointed out the capability of TiO_2 to favor the decomposition of HA, with subsequent formation of β-TCP and $CaTiO_3$, according to the following reaction:

$$Ca_{10}(PO_4)_6(OH)_2 + TiO_2 \rightarrow 3\,Ca_3(PO_4)_2 + CaTiO_3 + H_2O\uparrow \quad (1)$$

In particular, good cell adhesion and proliferation in contact with bulk TCP/TiO_2 composites were reported [50]. This finding was also confirmed by Hu et al. [47] and Sato et al. [48], which reported good cell behavior in contact with coatings of similar compositions.

4. A focus on calcium phosphate/titania bulk composite materials

Most studies have been devoted so far to the investigation of calcium phosphate sintering and the mechanical properties of pure TCP or the pure TiO_2. However, a little work has been reported on the performances of TCP-TiO_2 composites [28, 52, 53]. These papers focused on the synthesis of TCP-TiO_2 composites where titania nanoparticles could enhance the mechanical properties of calcium phosphate matrices, without penalizing biocompatibility.

In particular, Sprio et al. proposed a pressureless air sintering of mixed hydroxyapatite and titania (TiO_2) powders [28]; the sintering process was optimized to achieve dense ceramic bodies consisting in a bioactive/bioresorbable β-TCP matrix reinforced with defined amounts of submicron-sized titania particles.

A crucial step in the development of ceramic composites is the control of particle size and the driving energy for thermal consolidation processes [54]. Indeed, homogeneous ceramic composites come from adequately prepared powder mixtures, possibly preventing particle agglomeration. In this respect, HA powder was calcined at 900°C to increase the particle size whereas reducing surface activity possibly promoting the formation of particle clusters and to promote the achievement of composites with homogeneous microstructure [55]. On the other hand, an excessive increase of the HA particle size can reduce the driving energy for further HA grain growth during sintering, thus resulting in limited consolidation [54]. This comes very relevant when designing materials for load-bearing applications which need improved mechanical properties.

Therefore, a detailed study of the phase composition of HA/TiO_2 mixtures with temperature was mandatory; several mixtures were prepared (HA/TiO_2 = 90:10, 80:20, 70:30 vol%) and treated at different temperatures. As a general rule, the starting phase composition remained unchanged upon firing at temperatures up to 700°C, where the transformation of anatase into rutile started to take place; at higher temperatures, anatase underwent progressively increasing transformation in rutile and completely disappeared at 850°C. Therefore, even though titanium dioxide is present in different polymorphs, this does not result as a drawback, as above certain temperatures, of interest for ceramic sintering; the thermodynamically stable phase is always rutile.

As induced by the presence of rutile, the decomposition of HA phase into β-TCP occurred at relatively low temperatures (950°C); in the same temperature range, the formation of perovskite ($CaTiO_3$) was also detected. At higher temperatures, the phase composition of the mixture resulted unchanged up to 1250°C, when part of β-TCP was converted into the high-temperature polymorph α-TCP [56]; the raising of the firing temperature up to 1300°C promoted a further increase of the α-TCP content. Therefore, despite the highest volume shrinkage was detected at 1300°C by dilatometric analysis, the final sintering temperature was limited to 1250°C. Indeed,

as α-TCP is characterized by very high solubility in physiological environment [56], its presence may result in excessively fast resorption in vivo, hindering an adequate bone regeneration process. Moreover, the transformation of β-TCP in α-TCP is associated with an average 10% volume increase, which potentially penalizes the mechanical performances by micro-damages. A full consolidation of the composites was obtained by applying a dwell time of 1 h.

On this basis, the reinforcing mechanisms of titania particles embedded in the sintered composites were investigated by scanning electron microscopy, thus revealing that the presence of different amounts of titania does not strongly influence grain growth. Moreover, the spatial distribution of the submicron grains of titania (the brighter areas) could be still recognized also showing that, in high concentrations, they tended to coalesce in an interconnected framework (**Figure 3**).

The increase of mechanical properties was shown to depend strongly on the amount of titania particles introduced in the calcium phosphate matrix (**Figure 4**) [28].

Due to the different mechanical and thermal properties of the constituent phases, possible toughening mechanisms operating in these composites are crack deflection [57], crack bowing [58], residual stress [59], and microcracking toughening [60].

The Knoop hardness increased almost linearly with the content of TiO_2, as this phase is much harder than β-TCP. In literature, hardness is reported to be 10 GPa for TiO_2 [61] and 3.43 GPa for β-TCP [62].

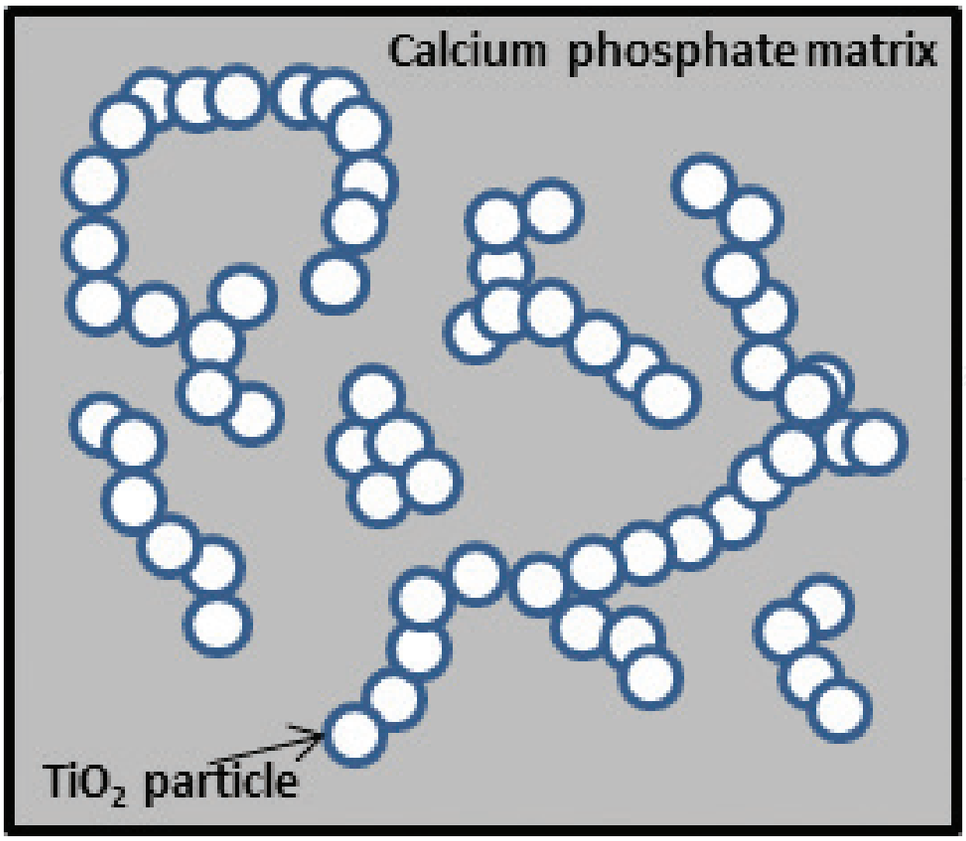


Figure 3. Schematic representation of the TCP/TiO_2 composite microstructure, evidencing the interconnection of TiO_2 grains.

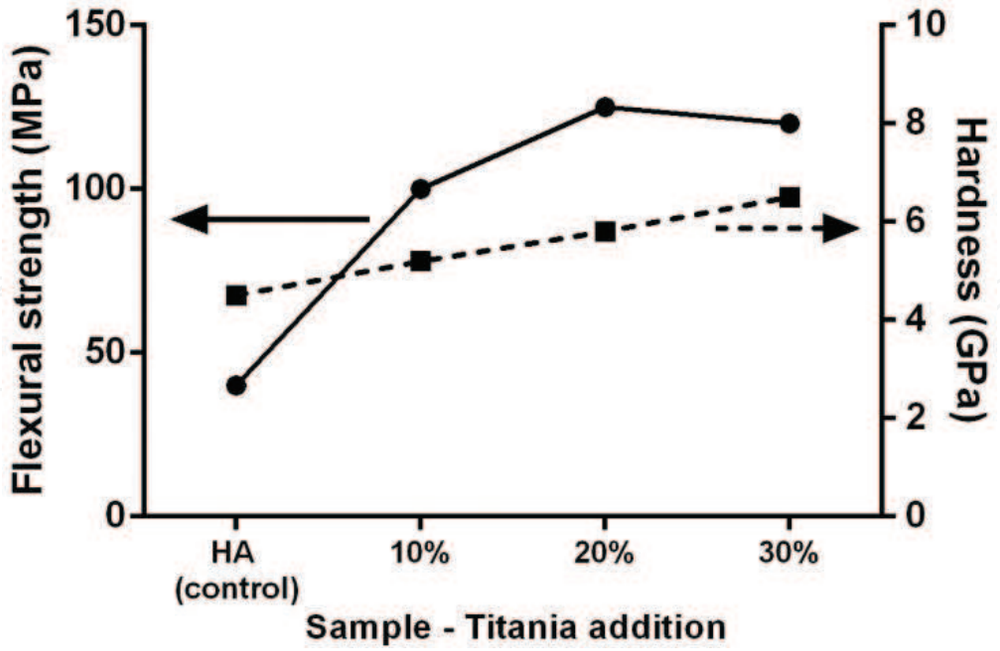


Figure 4. Plot of the flexural strength and Knoop hardness as a function of initial TiO_2 content.

TiO_2-based composites exhibited mechanical properties compliant with those of human cortical bone [33]. In this respect, the sample containing about 20 vol% of TiO_2 was of particular interest, as it represented the maximum level for successful strengthening of the final composite, at least in the range 0–30 vol% (**Figure 4**). This was attributed to a reduced number of microstructural defects, unavoidably generated by adding excessive amounts of titania. With the aim to develop porous bioactive scaffolds, the achievement of good mechanical properties by introducing limited amounts of bioactive, but nonresorbable, reinforcing components is a relevant point that place TCP/TiO_2 composites as very promising materials for the regeneration of load-bearing bone segments.

5. Designing porous calcium phosphate/titania scaffolds exploiting direct foaming method

Regeneration of load-bearing bone segments is still an open challenge due to the lack of biomaterials mimicking natural bone with suitable physicochemical and mechanical performance. Additionally, bone scaffolds should exhibit wide open and interconnected porosity, which however could strongly penalize the mechanical strength. Therefore, the research on adequate methods for porous ceramic development is today a hot topic in materials science [9].

Among the several processes proposed in literature to produce porous ceramics [63, 64], template-free foaming techniques are particularly promising, especially due to the absence of large amounts of organic phases to be eliminated during thermal consolidation. Indeed, forming techniques, making use of sacrificial templates, require long and slow thermal treatments to eliminate the organic component, possibly yielding structural damage and penalization of the final mechanical properties.

In particular, the direct foaming method was stated to be a low-cost and easy process that can provide pore volumes in the range 40–97% by incorporating air into a ceramic suspension that is subsequently dried and sintered. It was also reported that cellular structures prepared by direct foaming usually exhibit considerably higher mechanical strength than those obtained by other template-based techniques, mainly due to the strongly reduced occurrence of flaws in the cell struts [64, 65]. The decisive step in direct foaming methods is related to the development of ceramic slurries with optimal rheological properties, so that they can be dried and physically stabilized upon pouring into preshaped containers, while maintaining the shape, size, and distribution of the air bubbles.

This method was successfully applied to the synthesis of ceramic bone scaffolds made of β-TCP and TiO_2, developed from hydroxyapatite (HA) and TiO_2 powders, on the basis of the approach carried out by [23] exhibiting high and interconnected macroporosity (>70 vol%).

As the foaming process is based on a concentrated ceramic suspension, rheological properties are a critical issue. Indeed, when applied on a simple mixture of HA and TiO_2 powders (see previous paragraph), phase separation occurred in the green ceramic body, thus resulting in scaffolds characterized by reduced structural homogeneity. Therefore, an alternative approach was needed to obtain homogeneous blends, for which the mixture was subjected to a thermal treatment at 1000°C with a dwell time of 1 h before applying the foaming process, to obtain a powder with homogeneous composition.

With this, the application of direct foaming process was feasible and successful in obtaining ceramic bone scaffolds exhibiting high and interconnected macroporosity (>70 vol%).

Direct foaming process resulted very interesting to generate highly porous ceramics, as described in Ref. [66]. As observed by scanning electron microscopy, the microstructure of foamed scaffolds was characterized by large pores in the range 700–900 μm, in turn containing smaller pores, which provide interconnection throughout the whole scaffold (**Figure 5**).

Such microstructure is ideal when it comes to enable extensive penetration of new bone and expressing, at the same time, remarkable strength. In fact the spheroidal pore morphology provides enhanced resistance against fracturing, whereas smaller pores can aid to develop an effective vascular network. In this respect, the lack of vascularization in critical-size bone defects was reported as among the most critical issues limiting the extent of bone regeneration [1].

Besides morphology, compositional aspects can play a relevant role in determining the mechanical properties. Indeed the compressive strength of the TCP/TiO_2 composite scaffolds resulted about 8 MPa, with 75% porosity, i.e., thrice than the reference HA scaffolds. Together with Young's modulus, these composites thus exhibited mechanical properties in the range of cancellous bones (i.e., compression strength, 2–12 MPa; Young's modulus, 0.05–0.5 GPa). The enhanced mechanical competence was also associated to superior biological performance in vitro. Osteoblast-like cells (MG63) cultivated on the scaffold surface for 7 days covered almost completely the external surfaces of the scaffolds, and most of the macropores were completely infiltrated by cells, demonstrating high biocompatibility and osteointegrative potential as well [33].

Furthermore, an increase in cell proliferation was detected during 2 weeks of analysis, whereas the analysis of alkaline phosphatase (ALP) activity revealed a higher osteogenic activity for

β-TCP/TiO_2 scaffolds (**Figure 6**). This improvement could be related to both the higher solubility of TCP that yielded enhanced release of calcium ions to cells and also the presence of TiO_2 that in physiological environment can be promptly covered by a layer of HA.

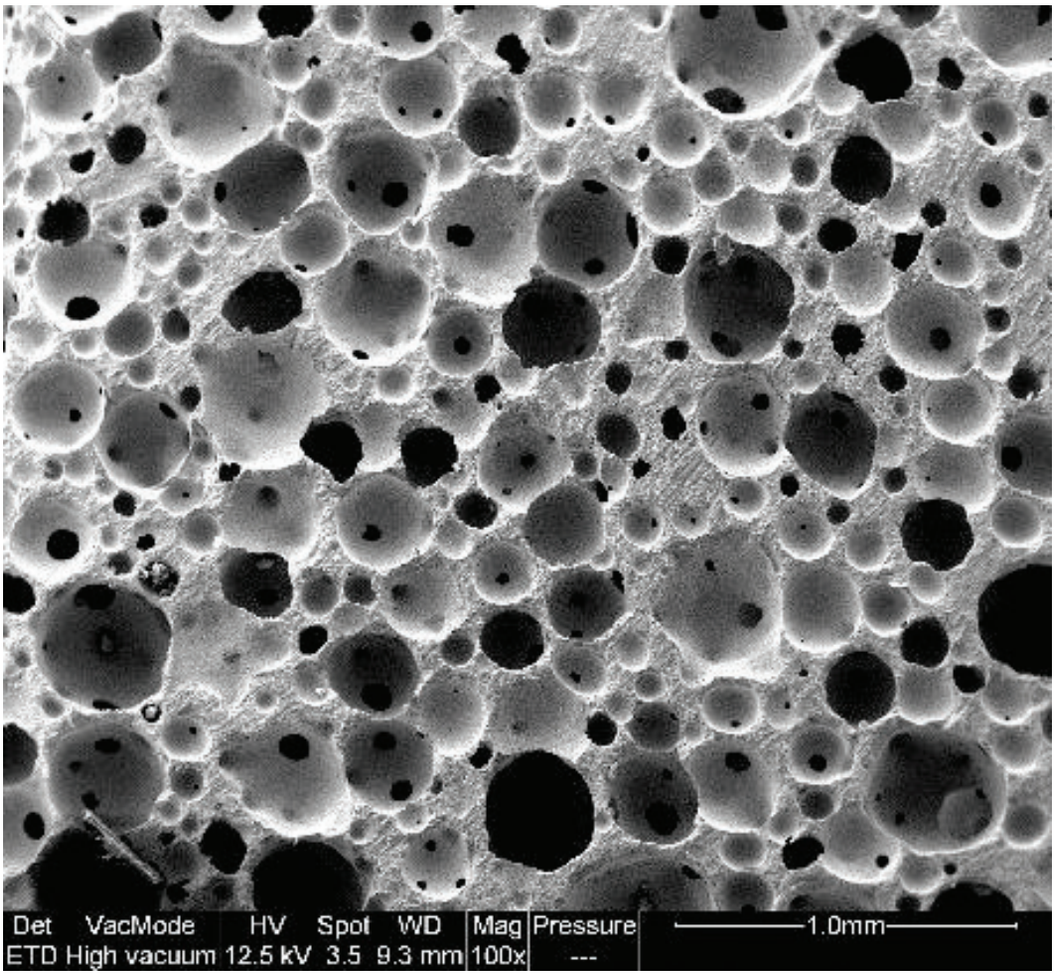


Figure 5. Porous microstructure of sintered porous TCP/TiO_2.

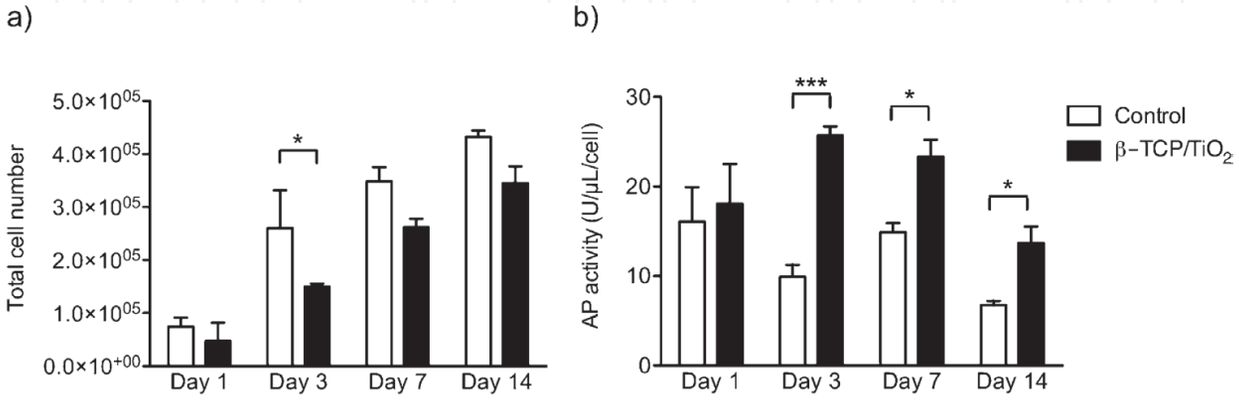


Figure 6. Proliferation of MG-63 osteoblast-like cells (a) and alkaline phosphatase (ALP) activity (b) when seeded on β-TCP/TiO_2 scaffolds and HA control [66].

6. Conclusions and future perspectives

The presented results show that porous scaffolds with bone-like composition and strength can be developed, by following approaches based on ceramic composite development. In particular, TiO_2 is a promising material as bioactive reinforcing phase for calcium phosphate matrices, giving its high biocompatibility. In respect to the design and development of adequate ceramic compositions, the challenge is still open as the settling of ceramic systems requires optimization of a variety of parameters related to initial composition, preliminary powder processing, forming methods, and sintering, all of which are crucial for the final biologic and mechanical properties. In this respect, direct foaming is a very promising method for porous scaffold development that can be flexibly applied to a variety of compositions. Therefore, the application of such process can be decisive for the development of reinforced scaffolds; in this respect, TiO_2-based scaffolds were still investigated in a limited extent, in spite of their potential to chemically and mechanically assist the regeneration of bone tissue defects, particularly load-bearing bone segments, as no regenerative solutions still exist in this field.

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