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Participation of Calcium Phosphate Bone Substitutes in the Bone Remodeling Process: Influence of Materials Chemistry and Porosity

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Abstract. Given the bone tissue's superb ability to adapt its mass and morphology to *in vivo* functional necessities, its aptitude to repair itself without leaving a scar, and its capacity to rapidly mobilize mineral supplies on metabolic demand, it is in fact the ultimate "smart" material in biological systems. Scientific efforts which may eventually lead to the synthesis of materials that mimic the *natural bones* have started about four decades ago [1, 2], and it should openheartedly be confessed now that the calcium phosphate-based synthetic bone substitute materials are still too far away from taking over the *golden standard* status of autologous bone chips/grafts which are harvested in real time, from the patient together with the bone marrow and living cells, during the surgery.

Requirements. Considering the ever-growing number of patients who suffer from devastating disorders of the skeleton, it becomes more critical for the material scientists to be able to design bone substitutes which can:

1) readily take part in bone remodeling (i.e., osteoconduction: the direct anchorage of an implant by bony tissue surrounding it, without the growth of fibrous tissue at the bone-implant interface),
2) itself cause the formation of bone tissues (i.e., osteoinduction), even if it is not in interfacial contact with natural bones,
3) maintain their mechanical strength even during the intermediate stages of cellular (i.e., osteoclasts) or active resorption, and
4) be *gradually* but fully replaced, within 48 to 52 weeks, by new bone (i.e., osseointegration) at the implantation site.

Unfortunately, until now, there are no synthetic biomaterials which simultaneously satisfy all of these criteria.

Bone Mineral. Bone mineral has commonly been referred to the perfectly stoichiometric compound *calcium hydroxyapatite* [$Ca_{10}(PO_4)_6(OH)_2$], but this can be a dangerously misleading oversimplification of the bone mineral. Actually it is a defective and rather complex substance (also doped with several mono- or divalent cations (Na, K, Mg, Zn, Fe, etc.) as well as with carbonate ions) with a generic formula of $Ca_{8.3}(PO_4)_{4.3}(HPO_4, CO_3)_{1.7}(OH, CO_3)_{0.3}$ [3, 4]. Therefore, bone mineral is not simply hydroxyapatite.

Bone Remodeling. Bones contain three distinct types of cells: the matrix-forming *osteoblast*, the tissue-resorbing *osteoclast*, and the *osteocyte* [5]. Osteoblasts are the cells present in bones which actually build the extracellular matrix and regulate its mineralization. The lifespan of an osteoblast ranges up to 8 weeks in humans, during which time it lays down 0.5 to 1.5 μm osteoid per day [5, 6]. Cells named as osteoclasts, on the other hand, are able to resorb fully mineralized bone as they are equipped with a variety of enzymes which lower the local pH to values between 3 and 4. Osteocytes are the principal (they account for about 90% of all cells in the adult skeleton) cells present in adult bones, and their special construction may actually orchestrate the spatial and

temporal recruitment of the cells that form and resorb bone. Modeling is the processes whereby bone is laid down onto available surfaces, and in the case of *remodeling*, osteoclastic resorption of bone leaves pockets that are then filled by osteoblast activity [5]. When the bones no longer have any osteoblasts or osteoclasts, all the modeling/remodeling processes would cease.

Bone Substitutes. Calcium phosphate-based bone substitute materials should ideally be implanted with the design consideration that the osteoclastic resorption will be able to slowly and gradually degrade the bone substitute material, and in the pockets created by the osteclasts, new bone will be deposited by the osteoblasts [5]. If a material is not resorbed by the osteoclasts (such as, crystalline alumina), then it can not be used as a bone substitute bioceramic, which can take part in bone turnover. On the other hand, if an implant material is simply soluble in physiological fluids (such as, Plaster of Paris), then it also can not help much in the bone remodeling processes, due to the lack of that precise interaction and crosstalk which must be present between the *resorbing* osteoclasts and *depositing* osteoblasts.

Resorbability. It is known that stoichiometric synthetic hydroxyapatite ceramics do not participate actively in bone remodeling, but they can only display *osteoconductive* behavior [7]. In other words, bone can grow in close contact with the stoichiometric hydroxyapatite implant interfaces, but hydroxyapatite ceramics can not be resorbed by the osteoclasts [8]. In the biomineralization processes, the bone mineral forms plate- or needle-like calcium-deficient hydroxyapatite crystals 100-150 nm in length and 10-20 nm thick (Fig. 1), and since it is less perfect in structure, and therefore, being more reactive and soluble, it facilitates chemical turnover or bone remodeling.

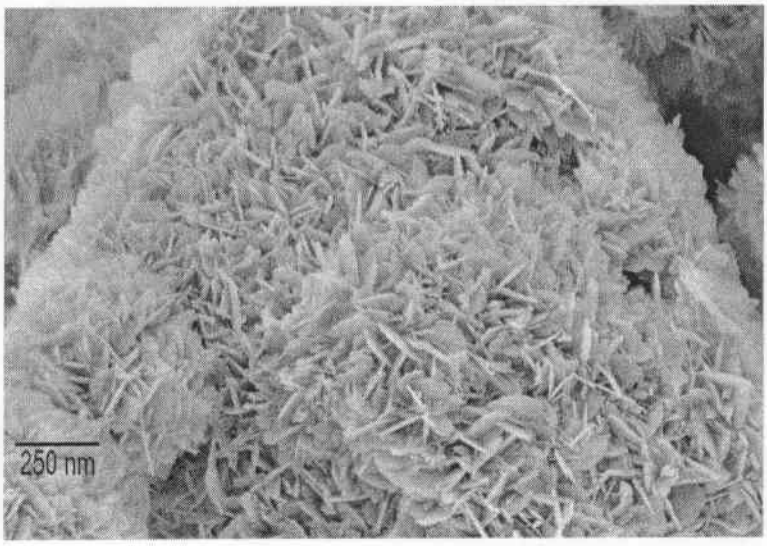

Figure 1. Ca-deficient hydroxyapatite nanoplates grown on a calcium phosphate ceramic in body fluid

Active resorption of the bioceramic implant, by the osteoclastic action, is a crucial condition if the *in vivo* biological participation of the material in bone remodeling is desired. Therefore, any biomaterial left in the human body must be considered as a potential focus for infection [8].

Porosity. For the osteoclasts to attack the bulk of the implanted ceramic, the material must have *interconnected* porosity (between 55 to 70%), and the pore sizes must be over the range of 150 to 700 μm [9], just like the natural bones. This porosity facilitates the complete (i.e,, both bulk and the

surface) invasion of the implant by the osteoclasts and osteoblasts from the very beginning, leading to *osseointegration* and further *vascularization*. If the material does not have the stated porosity, osteoclasts can only degrade the external surface of the implant, and this initial surface attack lasts for a relatively short period of time and then it may stop, if the osteoblasts regard the material as a foreign body.

Material Chemistry. However, porosity alone is not enough to allow the implant to show the ability of resorbability and participating in bone remodeling. A good example to this situation can be seen in the case of commercially available porous blocks or granules, which were manufactured from the trabecular bones of animal (bovine) origin [10, 11]. These materials are able to perfectly retain the magnificent porosity present in bovine bones, but since they are sintered at temperatures above 1200°C (to safely burn out the organic residues), they simply lose the material chemistry aspects of the original bones, and they convert into well-crystallized calcium hydroxyapatite, contaminated with only trace amounts of phases like CaO, $Ca_3(PO_4)_2$, and $Ca_4(PO_4)_2O$. Since the material after sintering is the *ceramic* and crystalline phase of hydroxyapatite, these samples were shown to be non-resorbable even after several years of implantation. With these kinds of blocks used in defect filling applications, it was seen that the bone ingrowth is perfect but the implant stayed as a foreign material. Moreover, a ceramic bone substitute which sits in the bone for long years without being resorbed, will be a potential spot for the development of an inflammatory response. However, when the same porous bovine hydroxyapatite ceramic blocks were first blended with human bone marrow cells and then implanted *in vivo*, it was observed that the material showed positive signs of participating in *osteogenesis* and remodeling processes [12].

Challenges. The bone mineral which embrace about 70 wt% [13] of human bones

(1) is not a crystalline ceramic,
(2) is not stoichiometric,
(3) is a complex and rather defective material,
(4) is not soluble in physiological fluids, but can only be degraded, when necessary, by the osteoclastic environment,
(5) contains elements like Na, K, Mg, Sr, Zn, and Fe in differing but small percentages,
(6) resembles to *hydroxyapatite*, but both the A- and B-sites of the bone mineral are partially doped with phosphate and carbonate ions,
(7) has its Ca-sites minimally doped with the above-mentioned cations,
(8) has a unique crystal structure [14] which places the hydroxyl and carbonate ions on its cell edges for easier chemical interaction with the surrounding cells and tissues, and
(9) the unit cell parameters of human bone mineral, as well as its overall Ca/P atomic ratio, display fluctuations as a function of bone maturation [15-17].

Predictions and Speculations. Hydroxyapatite-like bioceramics designed to mimic the bone mineral and intended for use in *in vivo* implantations should not possess steps of *heating/firing/calcination* at or above 650°C in any phase of their processing, manufacturing and shaping operations. The reason for this is so clear that at or above the stated temperature carbonate ions which may be present in the apatite structure are opt to readily leave the material [18]. The same also applies to the case of HPO_4^{2-} ions present in the bone mineral, and the materials chemist must face this challenge in preparing bioceramics which should resemble *the bone mineral* to the most possible extent. Sophisticated chemical techniques which involve the loading of several proteins, organic molecules, biopolymers or inorganic salts into the aqueous media of the synthesis reactors would become increasingly important in the manufacture of *next-generation macroporous* bioceramics.

The total weight percentage of Na, K, and Mg, which altogether amount to a value greater than 1 wt% in the bone mineral, must be considered in preparing synthetic bioceramic bone substitute materials [19]. Low-temperature (<100°C) chemical processing of calcium, sodium, and potassium phosphate and carbonate phases to be selected from a tentative list of chemicals, such as α-$Ca_3(PO_4)_2$, $Ca_4(PO_4)_2O$, $Ca_2P_2O_7$, $CaHPO_4$, $CaHPO_4{\cdot}2H_2O$, $Ca(H_2PO_4)_2{\cdot}H_2O$, $Na_4P_2O_7$, Na_2HPO_4, NaH_2PO_4, KH_2PO_4, K_2HPO_4, $NaHCO_3$, $CaCO_3$, K_2CO_3, and to be later processed in simulated body fluids [18], which contain trace amounts of Zn, Fe, and Cu ions [20], would probably yield bioceramics of higher resemblance to the bone mineral. Ca/P atomic ratio in the ideal synthetic bioceramic, as a tool of controlling resorbability, must be easily adjustable within the range of 1.30 to 1.60 by controlling the synthesis parameters. If the bioceramic undergoes *in vivo* osteoclastic resorption without a difficulty [21], then the Ca- and P-rich environment needed for *in situ* bone formation (i.e., *osteoinduction*) would have been provided even in the cases of intramuscular implantation.

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