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Bioresorbability, porosity and mechanical strength of bone substitutes: What is optimal for bone regeneration?

Gerjon Hannink [a], J.J. Chris Arts [b,*]

[a] Orthopaedic Research Laboratory, Department of Orthopaedics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
[b] Department of Orthopaedic Surgery, Research School Caphri, Maastricht University Medical Centre, Maastricht, The Netherlands

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ABSTRACT

Bone repair is a multi-dimensional process that requires osteogenic cells, an osteoconductive matrix, osteoinductive signalling, mechanical stability and vascularization. In clinical practice, bone substitute materials are being used for reconstructive purposes, bone stock augmentation, and bone repair. Over the last decade, the use of calcium phosphate (CaP) based bone substitute materials has increased exponentially. These bone substitute materials vary in composition, mechanical strength and biological mechanism of function, each having their own advantages and disadvantages. It is known that intrinsic material properties of CaP bone substitutes have a profound effect on their mechanical and biological behaviour and associated biodegradation. These material properties of bone substitutes, such as porosity, composition and geometry change the trade-off between mechanical and biological performance. The choice of the optimal bone substitutes is therefore not always an easy one, and largely depends on the clinical application and its associated biological and mechanical needs. Not all bone graft substitutes will perform the same way, and their performance in one clinical site may not necessarily predict their performance in another site. CaP bone substitutes unfortunately have yet to achieve optimal mechanical and biological performance and to date each material has its own trade-off between mechanical and biological performance. This review describes the effect of intrinsic material properties on biological performance, mechanical strength and biodegradability of CaP bone substitutes.

Introduction

Annually, more than 2.2 million bone grafting procedures are performed worldwide.[1] The current gold standard for bone repair is the use of autologous bone grafts harvested from a remote site in the patient. A few of the many problems associated with autografts include donor site morbidity and the restricted availability.[2] In addition to autografts, success has been reported with the use of allografts. Like the autografts, these allografts are also limited in supply and there exists a risk of disease transmission and immune rejection. Despite the benefits of both autografts and allografts, the relative concerns over their use has led to the development of numerous synthetic bone substitutes.

One of the most promising groups of synthetic bone substitutes are calcium phosphate ceramics (CaPs). The most commonly used CaPs are hydroxyapatite (HA) and tricalcium phosphate (TCP) or an intrinsic combination of the two.[3,4]

The rationale for the development of CaPs has been their similarity in composition to bone mineral and their similarities in some properties of bone, such as biodegradability, bioactivity and osteoconductivity. Another important property of bone, interconnecting porosity can be introduced during the manufacturing process of CaPs. Besides these desirable properties, CaPs are known to have relatively low mechanical properties and are therefore mostly not suitable for application in load-bearing areas, as they do not provide sufficient structural support.[5] A proper understanding of these properties, both biological and mechanical, are critical for the successful application of CaPs as bone substitutes. In this review we describe and discuss the interaction between these properties in search of what is optimal for bone regeneration.

Bone cell–ceramic interactions

Although TCP and HA derived through thermal treatment do not exist naturally, they have been shown to induce a biological response similar to that of bone.[3,5] Cells attach to and engulf the CaPs, causing them to biodegrade in vitro and in vivo. CaPs allow osteoblast cells to attach, proliferate, and differentiate. Differentiating osteoblast cells produce collagen type I, alkaline phosphatase, proteoglycans, and matrix proteins, such as osteocalcin, osteopontin, and bone sialoprotein known to signify bone formation.[5] Cellular response is affected by the composition of

* Corresponding author. Tel.: +31 43 3874502.
E-mail address: j.arts@mumc.nl (J.J. Chris Arts).

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CaPs. For example, zinc from zinc containing tricalcium phosphate or fluoride (F) from F-apatite or carbonate-F-apatite have been shown to inhibit osteoclastic activity.[5,6] On the other hand, F in F-apatite or Mg or Zn and/or F or combination of the three ions in carbonate apatite matrix was shown in vitro to promote collagen production and phenotypic expression of proteoglycans and matrix proteins associated with bone mineralization. The formation of distinct resorption pits on HA and TCP surfaces in the presence of osteoclasts was also observed.[7,8] Factors that affect cellular response to CaPs include surface topography (roughness), geometry, composition, and particle size.[5]

Biodegradability

Ideally, the rate of resorption of CaPs is similar to the rate of new bone formation but for obvious reasons not any faster. In vivo biodegradability can be achieved by dissolution or is cell mediated. The population of cells responsible for the resorption of CaPs mainly consists of multinuclear cells and osteoclasts.[7,8] However, macrophages are involved in the phagocytosis of CaPs as well.[9] The speed of biodegradability and the cell type involved in the resorption process are determined by both material properties, such as Ca/P ratio, crystallinity, particle size, surface area, and porosity and the local biological environment, such as pH, the presence of cells, and H_2O content.[3] In general, CaPs consisting of TCP have higher degradation rates as compared to CaPs consisting of HA.[10]

Recently, new tools have been developed to assess the incorporation, remodelling, and resorption of biomaterials in patients. High-resolution peripheral QCT makes it possible to assess changes in bone and biomaterial/CaP structure and density in vivo/in situ with a relatively high (82 μm) resolution.[11] The low radiation exposure associated with this technique makes longitudinal follow-up in patients possible and will provide long-term clinical data of the incorporation, remodelling and resorption bone substitute materials over time. In addition, FEA models can be build from the QCT images to quantify changes in bone and bone graft substitute strength. Another, promising method to follow bone metabolism and blood flow in patients is 18F-fluoride PET scanning.[12,13] However, data on the long-term follow-up of CaP bone substitutes implanted in patients is still rather limited.

Pore size

Pores in calcium phosphate materials are necessary for bone tissue formation because they allow migration and proliferation of osteoblasts and mesenchymal cells, as well as vascularization. In addition, a porous surface improves mechanical interlocking (interdigitation) between the implant biomaterial and the surrounding natural bone, providing greater mechanical stability at this critical interface.[14]

Pore size can be divided in two different groups: microporous (<5 μm pores) and macroporous (>100 μm pores).[14,15] Microporosity and macroporosity are important for the bioresorbability of the material. In addition, macroporosity plays an important role in the osteoconductivity.[3,5]

The minimum recommended pore size for a bone substitute is 100 μm,[16] but subsequent studies have shown better osteogenesis for substitutes with pores >300 μm.[14,17,18] Smaller pores (75–100 μm) resulted in ingrowth of unmineralized osteoid tissue or were penetrated only by fibrous tissue (10–44 and 44–75 μm).[16] However, using laser perforation techniques and titanium plates, four different pore sizes (50, 75, 100 and 125 μm) were tested in rabbit femoral defects under non-load-bearing conditions.[19] Bone ingrowth was similar in all the pore sizes suggesting that 100 μm may not be the critical pore size for non-load-bearing conditions. A very interesting aspect of the effect of pore size on bone regeneration is the impact on the progression towards osteogenesis. Relatively larger pores favour direct osteogenesis, since they allow vascularization and high oxygenation, whilst smaller pores result in osteochondral ossification, although the type of bone ingrowth depends on the material itself and the geometry of the pores.[18,20]

Porosity

Many studies have demonstrated a greater degree and faster rate of bone ingrowth or apposition with percentage porosity; however, there still seems to be some dispute regarding the optimum "type" of porosity. The rate and quality of bone integration have been related to a dependence on pore size, porosity volume fraction, and interconnectivity, both as a function of structural permeability and mechanics.[21] Bone regeneration in a scaffold in vivo involves recruitment and penetration of cells from the surrounding bone tissue, as well as vascularization. Higher porosity is expected to enhance osteogenesis and numerous studies have verified this hypothesis. These results were likely due to the larger surface area that resulted in higher ion exchange and bone-inducing factor adsorption.[10,21] There are a limited number of reports in the literature that show no effect of porosity on the amount of apposited bone.[22,23] The absence of any reports on the beneficial effects of lower porosity scaffolds in vivo solidifies the requirement of highly porous implants for bone regeneration.

Microporosity results in larger surface area that is believed to contribute to higher bone inducing protein adsorption as well as to ion exchange and bone-like apatite formation by dissolution and reprecipitation.[21] Surface roughness enhances attachment, proliferation and differentiation of anchorage dependent bone forming cells.[5]

High porosity and large pores enhance bone ingrowth and osseointegration of the implant after surgery.[14] Although there are a few reports in literature showing no difference in the osteogenic outcome for scaffolds with different porosities, there are no reports indicating a beneficial effect for implants with low porosity. Other factors, such as the rate of degradation and the mechanical performance of the scaffold should be taken into account when porosity is assessed.

Interconnectivity

Another important factor that determines the effectiveness of porosity is the structure of the pores with respect to each other. The pores may either be interconnecting or they contain "dead-ends".[15] Interconnecting macroporosity is introduced by adding porogens, such as naphthalene, H_2O_2, polymeric porogens or using the foaming method.[4] Microporosity depends on sintering temperature or sintering program. CaP sintered at 1200 °C shows significantly less microporosity than that sintered at 1000 °C and a dramatic change in crystal size.[5]

In general, calcium phosphates with interconnective pores are advantageous over biomaterials containing dead-end pores, because a spatial continuous connection of the pore system has a decisive meaning for the ingrowth of new bone, especially in long-term tissue interface maintenance.[15] However, when used in combination with osteogenic cells, materials containing interconnective pores are less able to contain osteogenic cells, resulting in a longer period until the pore space has been filled with newly formed bone.[24]

Biomechanical properties

The property that is most often used to characterize the mechanical behaviour of bone substitutes is their compressive

strength. Since these materials are intended to be used as bone substitutes, it is important to keep in mind that the compressive strength of human cortical bone ranges between 90 and 230 MPa (with tensile strengths ranging from 90 to 190 MPa), whereas the compressive strength of cancellous bone ranges between 2 and 45 MPa.[25,26]

Calcium phosphates generally provide limited biomechanical support, because they are brittle and have little tensile strength. TCPs are less brittle compared with HA. However, the faster degradation of TCP results in subsequent quicker loss of mechanical strength over time.

Although increased porosity and pore size facilitate bone ingrowth, the result is a reduction in mechanical properties, since this compromises the structural integrity of the scaffold. Moreover, scaffolds fabricated from ceramics with a high degradation rate should not have high porosities (>90%), since rapid depletion of the material will compromise the mechanical and structural integrity before substitution by newly formed bone.[14]

However, there is an upper limit in porosity and pore size set by constraints associated with mechanical properties. An increase in the void volume results in a reduction in mechanical strength of the scaffold, which can be critical for regeneration in load-bearing bones. For example, an increase of the total porous volume from 10 to 20% results in a factor four decrease in mechanical strength.[15,27]

The extent to which pore size can be increased whilst maintaining mechanical requirements is dependent on many factors, including the nature of the material and the processing conditions used in its fabrication.

Bioactivity, osteoconductivity and osteoinductivity

Bioactivity is defined as the property of materials to develop a direct, adherent, and strong bonding with the bone tissue.[3] From a cellular perspective, bioactivity reflects the attachment and differentiation of osteogenic cells on ceramic surfaces.[24]

Osteoconductivity is the ability of a material to serve as a scaffold to guide formation of newly forming bone along their surfaces. Osteoinductivity is the inherent ability of a material to induce bone formation without the presence of osteogenic factors and is usually demonstrated by bone formation after implantation of these materials in an ectopic site.[28,29]

CaP materials are generally known to be osteoconductive but not osteoinductive. However, several CaP materials, such as porous synthetic and coralline HA, β-TCP, and calcium phosphate cements, have been shown to have to ability to form bone in ectopic sites in different animals without the addition of osteogenic factors. The osteoinductive properties of these materials appear to be based on their architectural features, such as surface geometry, topography, pore size, and porosity which allow entrapment and concentration of circulating BMPs in the biologic fluid.[3,5,30,31] The main challenge remains to determine the appropriate architecture for these materials to optimize the ability to entrap and concentrate growth factors and/or osteoprogenitor cells.

Independent of architectural features, CaPs or CaP-based composite materials combined with BMPs, osteoprogenitor cells, and bioactive proteins or peptides have been shown to enhance bone formation.[32–34] The main challenges for this so-called engineered osteoinductivity are to determine the optimal scaffold, the appropriate dose of osteogenic factors, and the controlled release of these factors for different applications.

Discussion

The idea of an optimal bone graft substitute usable in all clinical indications, although alluring, is an idle one. Most bone graft substitutes need to be inserted into a stable host site that contains adequate vascularity and an adequate source of osteoblast precursor cells. In an appropriate site, these graft materials are eventually resorbed and replaced by host bone. However, if the operative site is mechanically unstable or if there are inadequate cells or other host factors limiting bone healing, problems may occur. Co-morbidities of the patient, such as osteoporosis and/or diabetes, will also negatively influence the in vivo performance and capacity of the biomaterial to incorporate.

Therefore, the bone substitute of choice depends largely on the clinical application and its associated biological and mechanical needs.[35] It is sensible to assume that not all bone graft substitutes will perform the same way and that the validation of a bone graft substitute in one clinical site may not necessarily predict its performance in another location.[1,36] Non-invasive and non-destructive quantitative imaging modalities have become a useful tools in monitoring the performance of CaPs in different locations.[11–13]

The large variety of bone substitutes available on the market represents not only the different clinical needs and scenarios encountered, but also the diversity of the expected clinical outcomes. The surgeon has to assess the requirements of the bone defect to be grafted, think of the properties needed for repair, and ultimately choose the appropriate bone substitute and its associated surgical technique. The choice of the appropriate bone substitute scaffold should be based on several parameters having in mind that the gold standard remains the autograft.

Over the recent years, hybrid bone substitute materials have appeared on the market. Usually the basis is an osteoconductive TCP or HA calcium phosphate scaffold which has been combined with other compounds to enhance the mechanical or the biological performance.[37,38] Clinical studies involving the addition of growth factors, such as BMP-2 and BMP-7 to CaPs have demonstrated remarkable osteoinductive capacities.[39,40] The incorporation of such factors to create osteoinductive scaffolds remains a promising option. In the near future, complex combination products that include cells, growth factors, and/or gene therapy in combination with scaffolds with optimal geometries are likely to give surgeons more effective tools for defect/application specific bone repair.

Conflict of interest statement

The authors state that they received nothing of value with regard to this manuscript. There is no conflict of interest.

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