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Review article

Novel bioactive materials developed by simulated body fluid evaluation: Surface-modified Ti metal and its alloys

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ABSTRACT

Until the discovery of the bone-bonding activity of Bioglass by Hench et al. in the early 1970s, it had not been demonstrated that a synthetic material could bond to living bone without eliciting a foreign body reaction. Since then, various kinds of materials based on calcium phosphate, such as sintered hydroxyapatite and β-tricalcium phosphate have also been shown to bond to living bone. Until the discovery of the bone-bonding activity of Ti metal formed with a sodium titanate surface layer by the present authors in 1996, it had not been shown that a metallic material could bond to living bone. Since then, various kinds of surface-modified Ti metal and its alloys have been found to bond to living bone. Until the discovery of the osteoinduction of porous hydroxyapatite by Yamasaki in 1990, it was unknown whether a synthetic material could induce bone formation even in muscle tissue. Since then, various kinds of porous calcium phosphate ceramics have been shown to induce osteoinduction. Until the discovery of osteoinduction induced by a porous Ti metal formed with a titanium oxide surface layer by Fujibayashi et al. in 2004, it had been unclear whether porous metals would be able to induce osteoinduction.

These novel bioactive materials have been developed by systematic research into the apatite formation that occurs on surface-modified Ti metal and its related materials in an acellular simulated body fluid (SBF) having ion concentrations almost equal to those of human blood plasma.

Some of the novel bioactive materials based on Ti metal are already in clinical use or clinical trials, such as artificial hip joints and spinal fusion devices.

In the present paper, we review how these novel bioactive materials based on Ti metal have been developed based on an evaluation of apatite formation in SBF. Without the SBF evaluation, these novel bioactive materials would most likely never have been developed.

Statement of Significance

On the basis of systematic study of apatite formation on a material in a simulated body fluid, various kinds of novel bioactive materials possessing not only bone-bonding activity and but also various other functions such as bone growth promotion, antibacterial activity and osteoinduction have been developed. Some of them are already successfully applied to clinical applications or trials for artificial hip joints and spinal fusion devices. It is shown in the present paper how these novel bioactive materials have been developed.

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1. Introduction

Synthetic materials are typically encapsulated in fibrous tissue in order to isolate them from the surrounding tissues after implantation into the living body. This is a protective response against foreign materials. However, Hench et al. discovered in the early 1970s that certain glasses in the system Na_2O-CaO-SiO_2-P_2O_5 are able to come into direct contact and tightly bond with the surrounding bone without any fibrous tissue formation [1]. This was the first man-made material which was found to bond to living bone. Since then, various kinds of ceramics, such as sintered hydroxyapatite, β-tricalcium phosphate, Ceravital-type glass-ceramic containing apatite and glass-ceramic A-W containing apatite and wollastonite, have also been shown to bond to living bone [2]. They are called "bioactive materials" and clinically used as bone substitutes. However, they have generally performed poorly in terms of mechanical strength and/or fracture toughness. Among them, glass-ceramic A-W was shown to possess a higher mechanical strength but lower fracture toughness than human cortical bone. Consequently, they are not considered useful under load-bearing conditions [2].

Under load-bearing conditions, metallic materials such as stainless steel, Co-Cr-Mo alloys and Ti metal and its alloys have been used as bone substitutes because of their high mechanical strength and superior corrosion resistance [3]. However, even Ti metal and its alloys which exhibit the best biocompatibility, do not bond to living bone, and their fixation to the surrounding bone is not stable over an extended period of time. Can these metals be modified so as to possess bone-bonding activity? All the bioactive materials described above are based on calcium phosphate. Can materials other than calcium phosphate bond to living bone?

In order to answer these questions, the bone-bonding mechanisms of the bioactive materials described above were investigated. It was found under transmission and scanning electron microscopy that the four materials of Bioglass, sintered hydroxyapatite, Ceravital-type glass-ceramic and glass-ceramic A-W bonded to the living bone of rabbit tibia through an apatite layer that formed on their surfaces in the living body after implantation [4]. Only the resorbable β-tricalcium phosphate was observed to bond directly to the living bone. In contrast, A-W-type glass-ceramic A-W(Al), which did not bond to living bone because of a slightly different composition from that of A-W, did not form the apatite layer on its surface in the living body. It was assumed from these results that a material able to form an apatite layer on its surface *in vivo* bonds to living bone through the apatite layer, in that it is not resorbable [4].

The apatite layer that formed on the surface of the four kinds of bioactive materials *in vivo* was found to be rapidly reproduced in an acellular simulated body fluid (SBF) having ion concentrations almost equivalent to those of human blood plasma [4]. The A-W-type glass-ceramic A-W(Al), which did not bond to living bone, also did not form the apatite on its surface in SBF. It was concluded from these findings that the bone-bonding activity of a material can be evaluated by examining apatite formation on its surface in SBF, in so far as it is stable in the living body [4].

It should be noted here that SBF is thermodynamically unstable, since it is supersaturated with respect to the apatite. However, usually the apatite hardly precipitates in SBF at the normal body temperature, since the energy barrier for the homogeneous nucleation of the apatite in SBF is very high. It is only when a foreign material induces heterogeneous nucleation of the apatite on its surface by means of certain functional groups that the apatite is precipitated on its surface. A material that is able to precipitate the apatite on its surface in SBF also induces the apatite formation *in vivo* and subsequently bonds to living bone through the apatite layer.

In the simple CaO-SiO_2-P_2O_5 system, it was found that CaO-SiO_2 glasses formed the apatite on their surfaces in SBF in a short period of time and bonded to living bone through an apatite layer, whereas CaO-P_2O_5 glasses did not form the apatite on their surfaces either in SBF or *in vivo* and did not bond to living bone [5]. This indicates that the P_2O_5 is not an essential component required for the apatite-forming ability and bone-bonding activity.

The apatite formation on the surfaces of CaO-SiO_2 glasses is thought to occur as follows. The Ca^{2+} ions in the glasses are released via exchange with H_3O^+ ions in SBF, forming a silica gel layer on the surfaces of the glasses. The silica gel induces apatite nucleation. Once the apatite nuclei are formed, they grow by consuming the calcium and phosphate ions from the surrounding SBF [5].

In pure oxide systems, it was found that even pure silica and titania gels, respectively, were able to form the apatite on their surfaces in SBF in a short period of time [6]. This indicates that even CaO is not essential for apatite formation.

Ti metal and its alloys are usually covered with a thin titanium oxide layer. It would thus be expected that Ti metal and its alloys would also form the apatite on their surfaces in SBF as well as in living body so as to be able to bond to living bone when slightly modified.

Various kinds of surface modifications have been attempted to confer apatite-forming ability or bone-bonding activity on Ti metal and its alloys using various techniques, including ion implantation [7–9], electrochemical treatments [10–18] and hydrothermal treatments [19–23]. However, these techniques require special equipment and are not readily applicable to large-scale medical devices comprised of complex or porous structures. In contrast with these techniques, simple chemical and heat treatments do not have such limitations.

Various kinds of chemical and heat treatments also have been performed on Ti metal and its alloys [24–33]. However, in the published reports their apatite-forming abilities or bone-bonding activities were not fully investigated in terms of their surface structures. The present authors systematically applied chemical and heat treatments to Ti metal and its alloys. Their apatite-forming ability in SBF was analyzed in terms of the surface structure, while the bone-bonding activity was investigated in terms of apatite formation in SBF.

As a result, certain surface-modified Ti metal and its alloys were found to exhibit bone-bonding activity. Some of them exhibited not only the bone-bonding activity but other functions as well, such as bone-growth promotion and antibacterial activity. Some of the surface-modified porous Ti metals exhibited not only osteoconduction but also osteoinduction. Organic polymers such