Available online at www.sciencedirect.com

ScienceDirect

Journal of the European Ceramic Society 27 (2007) 1553–1558

www.elsevier.com/locate/jeurceramsoc

Titania-based bioactive materials

T. Kokubo *, T. Matsushita [1], H. Takadama [2]

Department of Biomedical Sciences, College of Life and Health Sciences, Chubu University, 1200 Matsumoto-cho, Kasugai 487-8501, Japan

Available online 18 May 2006

Abstract

Bioactive materials hitherto clinically used are based on silicate or phosphate. Recently, various kinds of bioactive materials with different mechanical properties are being developed on the basis of titania. A bioactive material with high fracture toughness was obtained by surface modification of titanium metal with an amorphous sodium titanate. An osteoinductive material with high mechanical strength was obtained by surface modification of porous titanium metal with anatase. A bioactive material with high flexibility was obtained by surface modification of polyethylene terephthalate fiber fabric with brookite. A bioactive material with analogous mechanical properties to those of human cortical bone was obtained by dispersing nano-sized anatase particles in a polyethylene. A bioactive material with self-setting property was obtained by mixing anatase particles with polymethyl methacrylate (PMMA) particles of a conventional PMMA cement.

Keywords: Composites; Mechanical properties; Apatite; TiO_2; Biomedical applications

1. Introduction

Some ceramics such as Bioglass,[1] Grass-Ceramic A-W,[2] sintered hydroxyapatite[3] and sintered β-tricalcium phosphate[4] have been shown to bond to living bone. They are called bioactive ceramics and already clinically used as important bone substitutes. They are, however, lower in fracture toughness and higher in elastic modulus than the human cortical bones. All of them are based on silicates or phosphates.

In 1994, titania gel was found to form a bone-like apatite on its surface in a simulated body fluid (SBF) with ion concentrations nearly equal to those of the human blood plasma, similarly to a silica gel.[5] It has been also shown that materials able to form the bone-like apatite on its surface in SBF produce the same kind of apatite on its surface in the living body and bond to living bone through the apatite layer.[6] Since these findings, various kinds of bioactive materials with different mechanical properties have been developed on the basis of titania. Titanates generally show higher elastic modulus and chemical durability than silicates and phosphates. Bioactive materials based on the titania are, therefore, expected to exhibit different properties from those of bioactive materials based on silicates and phosphates. Novel bioactive materials developed on the basis of the titania are reviewed in the present paper.

2. Bioactive material with high fracture toughness

Titanium metal and its alloys such as Ti-6Al-4V, Ti-15Mo-5Zr-3Al and Ti-6Al-2Nb-Ta with high fracture toughness were soaked in 5 M-NaOH solution at 60 °C for 24 h and then heat-treated at 600 °C for 1 h. A sodium titanate hydrogel layer with a graded structure within 1 μm in thickness was formed by the former NaOH treatment and stabilized as an amorphous sodium titanate layer by the subsequent heat treatment without substantial change in the graded structure, as shown in Fig. 1.[7]

The titanium metal and its alloys formed with the sodium titanate on their surfaces produced the bone-like apatite on their surfaces in SBF, as shown in Fig. 2.[8] The titanium metal first released Na^+ ions from its sodium titanate layer via exchange with H_3O^+ ions in SBF to form a lot of Ti-OH groups on its surface, as shown in Fig. 3.[9] As a result, the surface is negatively charged, to react with Ca^{2+} cations in SBF to form a calcium titanate. As the Ca^{2+} cations are accumulated, its surface is positively charged to react with phosphate anions to form an amorphous calcium phosphate. Since this phase is metastable, it is eventually transformed into stable crystalline bone-like apatite.

* Corresponding author. Tel.: +81 568 51 6583; fax: +81 568 51 6583.
E-mail addresses: kokubo@isc.chubu.ac.jp (T. Kokubo), matsushi@isc.chubu.ac.jp (T. Matsushita), takadama@isc.chubu.ac.jp (H. Takadama).
[1] Tel.: +81 568 51 9731; fax: +81 568 51 5370.
[2] Tel.: +81 568 51 6291; fax: +81 568 51 5370.

0955-2219/$ – see front matter
doi:10.1016/j.jeurceramsoc.2006.04.015

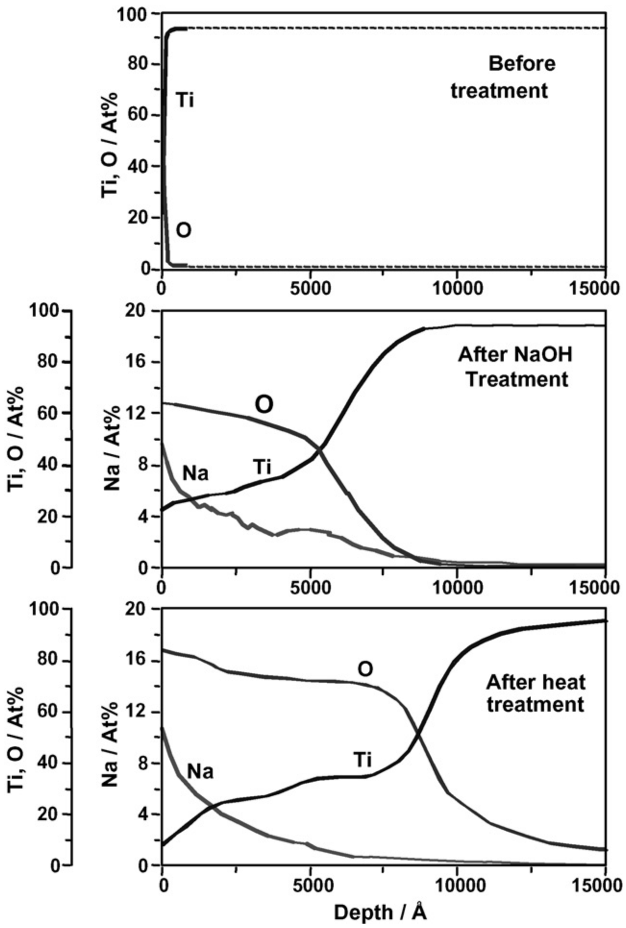

Fig. 1. Auger electron spectra profile of the surface of Ti metal untreated and those subjected to 5.0 M-NaOH treatment at 60 °C for 24 h and subsequent heat treatment at 600 °C for 1 h.

The titanium metal and its alloys surface-modified with the sodium titanate produced the bone-like apatite on their surfaces even in the living body, and tightly bonded to the living bone through the apatite layer, as shown in Fig. 4.[10] The bioactive sodium titanate layer was formed on the surface of macroporous titanium metal on artificial hip joint of a titanium alloy, as shown in Fig. 5, and successfully subjected to clinical trials for 70 patients.

3. Osteoinductive material with high mechanical strength

It was found that Na_2O-free titania gel induces apatite formation on its surface in SBF more effectively than the amorphous sodium titanate, when it takes crystalline anatase or rutile.[11] The anatase phase was formed on a surface of a porous titanium metal, which was prepared by a plasma spray method and contained 40–60 vol.% of interconnected pores 100–300 μm in size, by the following chemical treatments. The porous titanium metal was first soaked in 5 M-NaOH solution at 60 °C for 24 h to form a sodium titanate hydrogel layer on its surface, then soaked in a hot water at 80 °C for 48 h to remove the Na^+ ions from the sodium titanate gel layer and finally heat-treated at 600 °C for 1 h to transform the Na^+-free titania gel layer into the anatase layer.[12]

The porous titanium metal formed with the anatase on its surface produced bone tissue in its pores not only in a bone defect but also in muscle of beagle dog, as shown in Fig. 6.[13] The formation of the bone in the muscle was observed as early as 3 months after the implantation. This kind of osteoinductive property is considered to be an indication of high bioactivity. Such osteoinductive property has been reported for various kinds of porous calcium phosphate ceramics.[14] In comparison with the porous calcium phosphate ceramics, the porous titanium metal

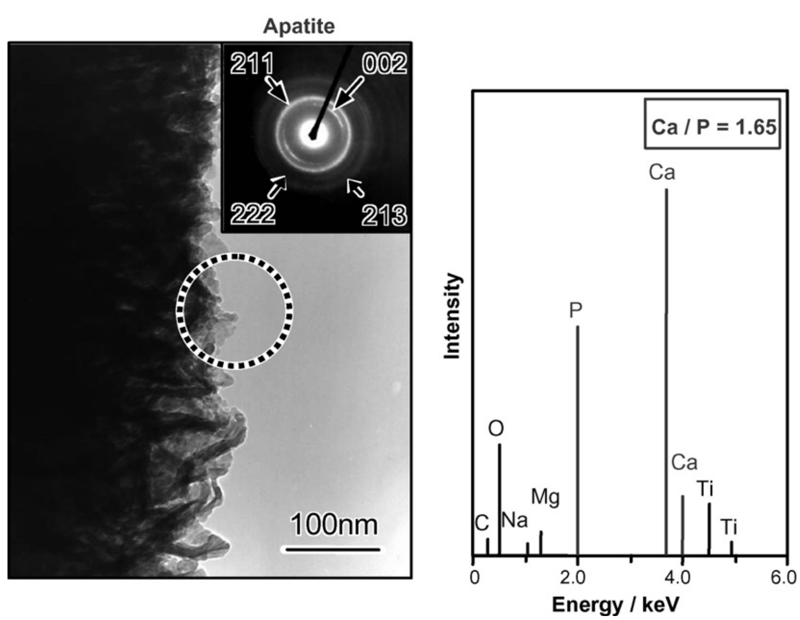

Fig. 2. Transmission electron micrograph (left) and energy dispersive X-ray spectra (right) of surface of NaOH- and heat-treated Ti metal after soaking in SBF for 5 days.

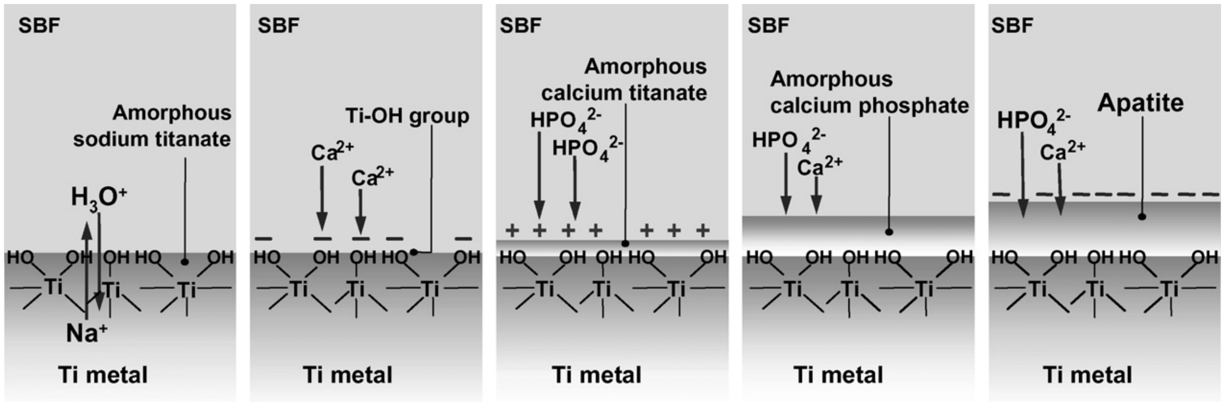

Fig. 3. Schematical presentation of apatite formation on NaOH- and heat-treated Ti metal as a function of surface charge variation.

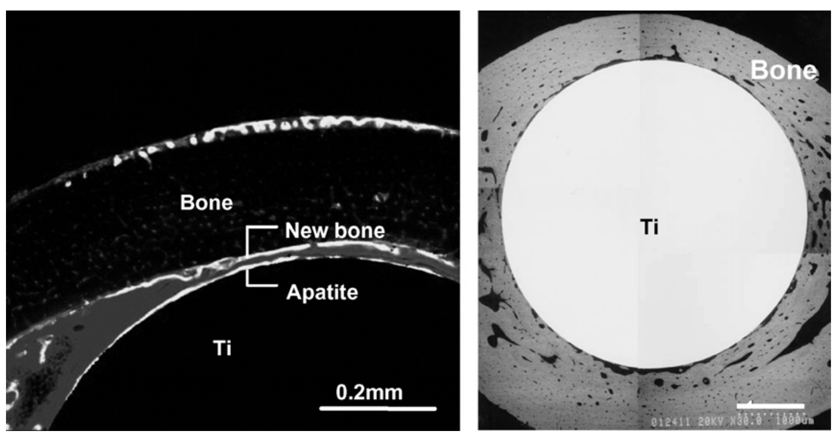

Fig. 4. Confocal laser scanning micrograph (left) and SEM phonograph (right) of cross-section of NaOH- and heat-treated Ti metal implanted into rabbit femur for 3 and 12 weeks, respectively.

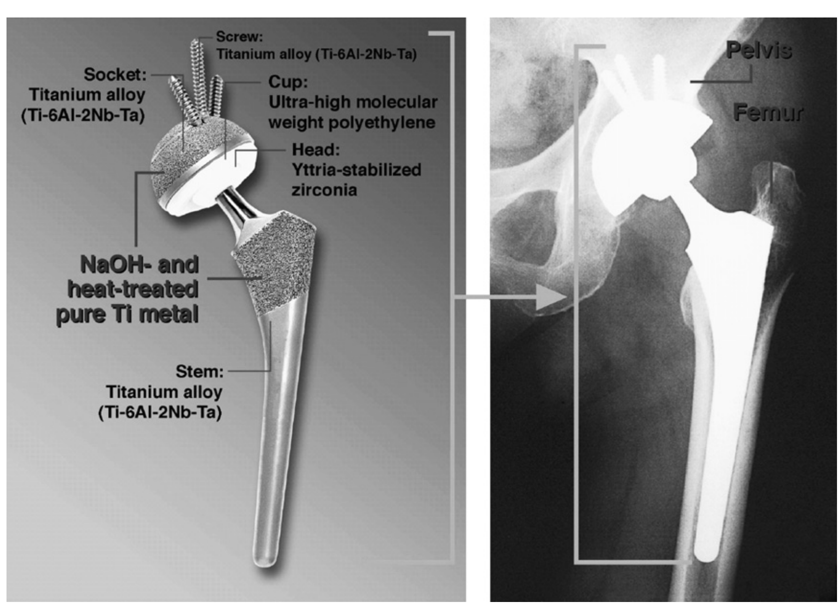

Fig. 5. Application of NaOH- and heat-treated Ti metal to hip joint.

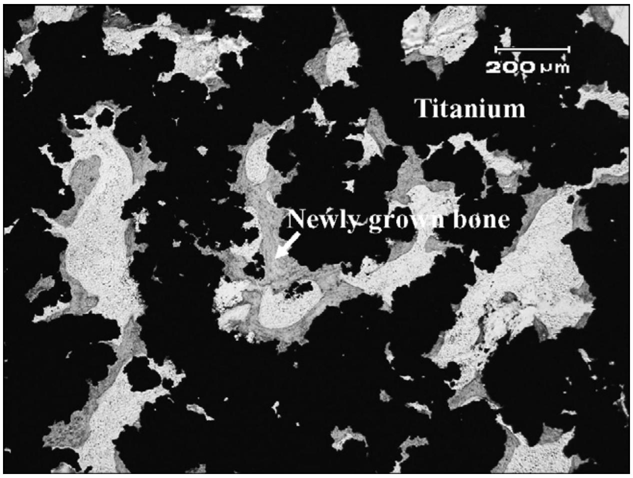

Fig. 6. Bone induction in porous Ti metal implanted into muscle of dog, 12 months after implantation.

modified with the anatase has much higher mechanical strength, and hence might be useful as bone substitutes even under load-bearing condition such as vertebrae.

4. Bioactive material with high flexibility

Two dimensional fabric of polyethylene terephthalate (PET) fibers was soaked in a titania sol solution, which was prepared by mixing titanium isopropoxide, ethanol, water and nitric acid in 1.0:18.25:1.0:0.1 in molar ratio, for 1 day, to form a titanium oxide layer on its surface, after pretreatment with 2 wt.% NaOH solution at 40 °C for 30 min to improve affinity of PET to the titanium oxide. It was then soaked in a water or 0.1 M HCl solution at 80 °C for 8 days. The titanium oxide as-formed on PET took an amorphous phase, but crystalline anatase and brookite phases, after the subsequent water and HCl treatments, respectively. The PET fabrics formed with the amorphous and the anatase-type titanium oxide on their surfaces did not form the bone-like apatite on their surfaces in SBF within 3 days, whereas that formed with the brookite-type titanium oxide produced the apatite uniformity on the surfaces of the individual fibers constituting the fabric in SBF within 3 days, as shown in Fig. 7.

The PET fibers can be fabricated into two or three-dimensional structures containing interconnected channels in various sizes. The PET fabrics surface modified with the brookite-type titanium oxide could induce apatite formation on the surface of the constituent fibers in the living body to integrate with the living bone through the apatite layer. This kind of bioactive materials with high flexibility is believed to be useful as bone substitutes even in bone defects with complex shapes.

5. Bioactive materials with analogous mechanical properties

A composite of hydroxyapatite with polyethylene has been known as a bioactive composite with analogous mechanical properties to those of the human cortical bone.[15] The hydroxyapatite more than 40 vol.%, however, cannot be incorporated into the polyethylene without loosing ductility of the composite. The resultant product shows lower bending strength and Young's modulus than human cortical bone.

Titanium oxide particles, anatase phase 200 nm in average size (Ishihara Sangyo Kaisha, Ltd., Mie, Japan), were

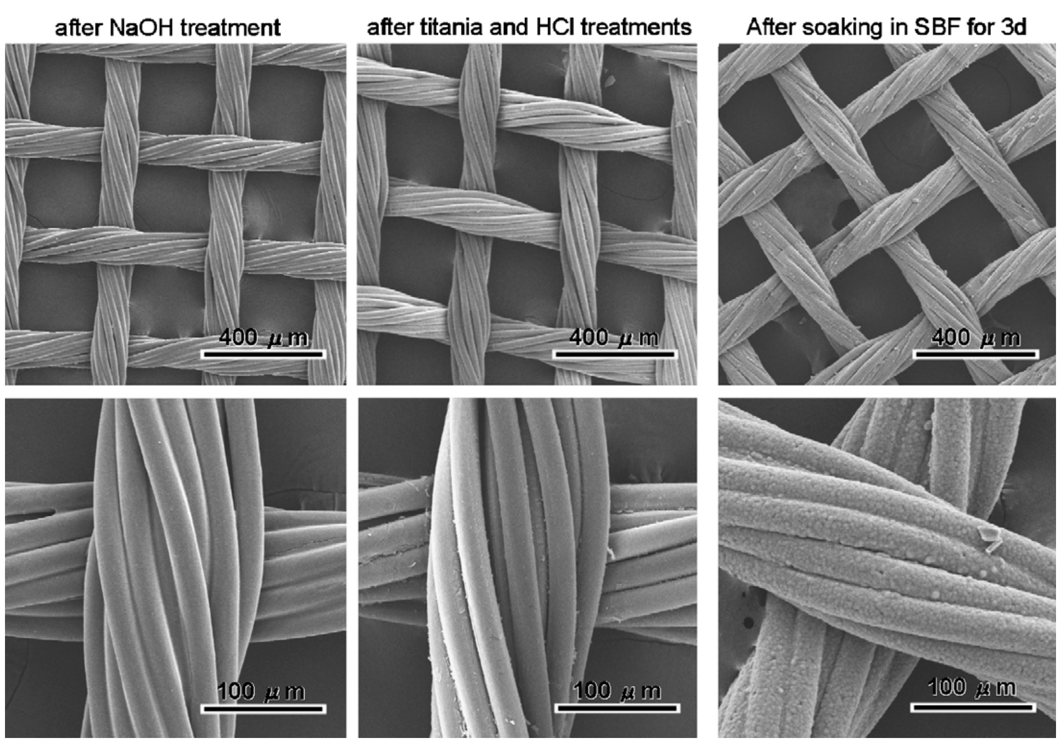

Fig. 7. SEM photographs of PET fiber fabric subjected to NaOH treatment, titania and HCl treatments and then soaked in SBF for 3 days.

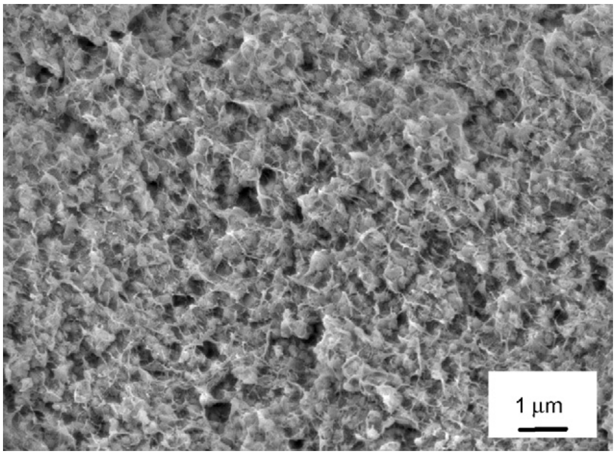

Fig. 8. SEM photograph of a composite in which 50 vol.% nano-sized anatase are dispersed in polyethylene.

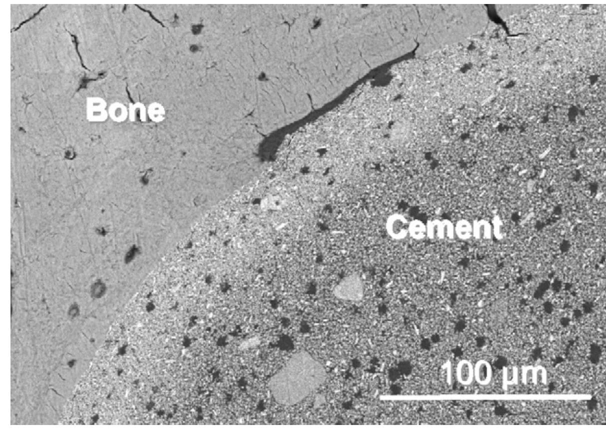

Fig. 9. Back-scattered electron image of interface between PMMA cement containing 55.6 wt.% TiO_2 and rat tibia, 12 weeks after implantation.

mixed with polyethylene (Japan Polyolefins, Tokyo, Japan) with number-average molecular weight of 1.2×10^4, heated to 210 °C, kneaded and pressed into a plate. The titanium oxide up to 50 vol.% were uniformly dispersed in the polyethylene, as shown in Fig. 8.

The composite containing 50 vol.% of TiO_2 showed a bending strength and Young's modulus of 68 MPa and 7.1 GPa, respectively. These values are in the range of those of the human cortical bone, 50–150 MPa and 7–30 GPa, respectively. It produced the bone-like apatite on its surface in SBF within 7 days. This composite has thermoplasticity and machinability, and hence might be useful as bone substitutes such as craniofacial implant.

6. Bioactive material with self-setting property

Titanium oxide particles of anatase-rutile mixed phases 2 µm in average size (Ishihara Sangyo Kaisha, Ltd., Mie, Japan) were mixed with polymethyl-methacrylate (PMMA) particles 5 µm in average size with average molecular weight of 270,000 and benzoyl peroxide as polymerization initiator. On the other hand, methylmethacrylate (MMA) monomer liquid was mixed with *N*,*N*-dimethyl-*p*-toluidine liquid as polymerization accelerator. The weight percent of TiO_2, PMMA and MMA were 55.6, 14.8 and 29.6. The amounts of the initiator and accelerator were 4 and 2 wt.% of MMA, respectively. When the powders and liquids were mixed, they were set within 9 min, which is almost equal to the setting time of a commercial PMMA cement, CMW1 (Depuy Co.). The maximum temperature during the setting reaction was 81 °C, which was lower than that of CMW1, i.e. 100 °C. The compressive and bending strength and Young's modulus of the set cement were 139 and 69 MPa, and 4.1 GPa, which were higher than those of CMW1, i.e. 88 and 59 MPa, and 1.6 GPa. The set cement produced the bone-like apatite on its surface in SBF within 3 days. When the mixture was injected to a hole of rat tibia, it directly bonded to the living bone within 12 weeks, as shown in Fig. 9. This kind of bioactive material with self-setting property as well as high mechanical strength and Young's modulus might be more useful as materials for fixing metallic components of artificial joints to the surrounding bone, as well as for percutaneous transpedicular vertebroplasty than the conventional nonbioactive PMMA cement.

7. Conclusions

Various kinds of bioactive materials with different properties from those of the conventional silicate and phosphate bioactive materials have been developed on the basis of titania and titanate. These new kinds of bioactive materials might be useful as bone substitute in various fields.

References

1. Hench, L. L., Splinter, R. J., Allen, W. C. and Greenlee, T. K., Bonding mechanism at the interface of ceramic prosthetic materials. *J. Biomed. Mater. Res. Symp.*, 1971, **2**, 117–141.
2. Kokubo, T., Shigematsu, S., Nagashima, Y., Tashiro, M., Nakamura, T., Yamamuro, T. *et al.*, Apatite- and wallastonite-containing glass-ceramics for prosthetic application. *Bull. Inst. Chem. Res., Kyoto Univ.*, 1982, **60**, 260–268.
3. Jarcho, M., Kay, J. L., Gumaer, R. H. and Drobeck, H. P., Tissue, cellular and subcellular events at bone-ceramic hydroxyapatite interface. *J. Bioeng.*, 1997, **1**, 79–92.
4. Rejda, B. V., Peelen, J. G. J. and de Groot, K., Tricalcium phosphate as a bone substitute. *J. Bioeng.*, 1977, **1**, 93–97.
5. Li, P., Ohtsuki, C., Kokubo, T., Nakanishi, K., Soga, N., Nakamura, T. *et al.*, A role of hydrated silica, titania and alumina in forming biologically active bone-like apatite on implant. *J. Biomed. Mater. Res.*, 1994, **28**, 7–15.
6. Kokubo, T., Design of bioactive bone substitutes based on biomineralization process. *Mater. Sci. Eng.*, 2005, **C25**, 97–104.
7. Kim, H. M., Miyaji, F., Kokubo, T., Nishiguchi, S. and Nakamura, T., Graded surface structure of bioactive titanium metal prepared by chemical treatment. *J. Biomed. Mater. Res.*, 1999, **45**, 100–107.
8. Takadama, H., Kim, H. M., Kokubo, T. and Nakamura, T., TEM-EDX study of mechanism of bonelike apatite formation on bioactive titanium metal in simulated body fluid. *J. Biomed. Mater. Res.*, 2001, **57**, 441–448.
9. Kim, H. M., Himeno, T., Kawashita, M., Lee, J. H., Kokubo, T. and Nakamura, T., Surface potential change in bioactive titanium metal during the process of apatite formation in simulated body fluid. *J. Biomed. Mater. Res.*, 2003, **67A**, 1305–1309.
10. Nishiguchi, S., Fujibayashi, S., Kim, H. M., Kokubo, T. and Nakamura, T., Biology of alkali- and heat-treated titanium implants. *J. Biomed. Mater. Res.*, 2003, **67A**, 28–35.

11. Uchida, M., Kim, H. M., Kokubo, T. and Nakamura, T., Apatite-forming ability of titania gels with different structures. *J. Biomed. Mater. Res.*, 2003, **64A**, 164–170.
12. Uchida, M., Kim, H. M., Kokubo, T., Fujibayashi, S. and Nakamura, T., Effect of water treatment on the apatite-forming ability of NaOH-treated titanium metal. *J. Biomed. Mater. Res. (Appl. Biomater.)*, 2002, **63**, 522–530.
13. Fujibayhashi, S., Neo, M., Kim, H. M., Kokubo, T. and Nakamura, T., Osteoinduction of porous bioactive titanium metal. *Biomaterials*, 2004, **25**, 443–450.
14. Barrere, F., van der Volk, C. M., Dalmezier, R. A. J., Meijer, G., van Blitterswijk, C. A., de Groot, K. *et al.*, Osteogenecity of octacalcium phosphate coatings applied on porous metal implants. *J. Biomed. Mater. Res.*, 2003, **66A**, 779–788.
15. Bonfield, W., Hydroxyapatite-reinforced polyethylene as an analogous materials for bone replacement. In *Annuals of the New York Academy of Science*, *Vol 523*, ed. P. Ducheynel and J. Lemons. New York Academy of Science, New York, 1988, pp. 173–177.