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POTENTIAL OF CERAMICS AS BIOMATERIALS

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Summary

Ceramics already play an unique and important role in repairing damaged bones, teeth and even soft tissues. Ceramics can not only substitute for the damaged tissues, but also destroy them in situ without excising and promote their self-repairing activities. Fundamental understanding of reactions of ceramics with living tissues has also largely progressed. This enables us to design new kind of ceramics with various functions for biomedical applications. Interests of medical scientists in ceramics are steadily increasing. Those of ceramic scientists in biomedical field is, however, not large. Social, economical and educational conditions must be changed for creamics to continue to grow in this field and contribute to welfare of human being.

1. Introduction

Probably 30 years ago, no one imagined that ceramics could play an important role in repairing damaged tissues of the human body. One of the most famous text book of ceramics, "Introduction to Ceramics" gave no mention about biomedical applications of ceramics even in its second edition published in 1976.[1)]

When we look at the structure of the tissues of the human body, however, we find that some tissues are mainly composed of an inorganic substance. In hard tissues such as bones and teeth, the hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) occupies 70 to 97% of their volumes.[2)] Therefore, it is expected that a certain kind of inorganic materials, i.e, ceramics could play better roles in repairing these tissues than any other kind of materials of metals and organic polymers. The hydroxyapatite in these tissues is intimately combined with organic substances such as collagen fibers. This indicates that a certain kind of ceramics could show good compatibility even with soft tissues consisting of only organic substances and hence repair them. Ceramics can also show various kinds of electromagnetic properties which are effective for destroying damaged tissues and promoting their self-repairing activities. Because of these characteristics, ceramics already play an important role in repairing damaged tissues of the

human body, and are increasing their importance in biomedical field. In the present paper, recent progress of ceramics as biomaterials and their feature aspects are briefly reviewed.

2. Nearly Inert Ceramics

The first scientific approach to biomedical applications of ceramics was done by Hulbert et al in late 1960s. They proved that porous alumina ceramics show so high compatibility with the bony tissues that the surrounding bone can penetrate into the pores, when their diameter are larger than 100 μm.[3]

On the basis of the following fundamental studies, a high density and high purity sintered alumina ceramic was first applied to the socket and head of the artificial hip joint by Boutin et al in 1970.[4] Until that time, the socket was made of a high molecular weight polyethylene, and the head of Co-Cr alloys or stainless steel. By using the alumina socket and head, occurrence of toxic debrises of metals and polyethylene was eliminated and the coefficient of the friction of the joint as well as the wear rates of both the socket and head were remarkably reduced, since the alumina shows high hardness and excellent chemical durability. Later, the alumina head was shown to give the low coefficient of the friction and the low wear rates even against to the polyethylene socket.[5] Both types of the hip joint are now widely clinically used. Figure 1 shows an example of their hip joints.

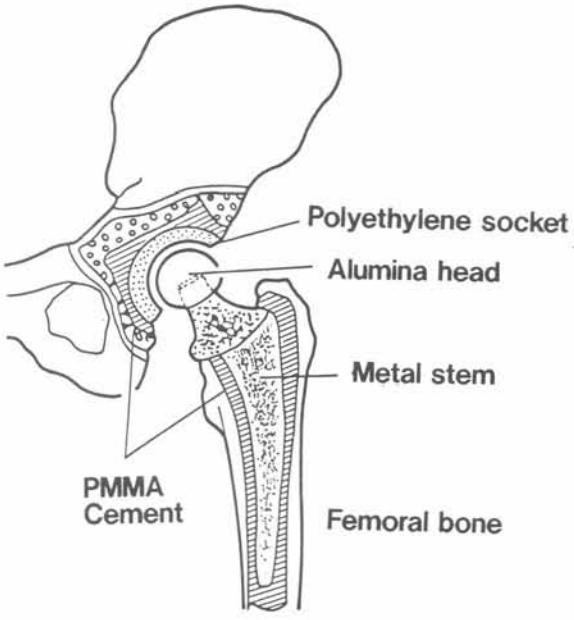

Fig. 1 Example of artificial hip joint using alumina head.

Because of the high biocompatibility and the high mechanical strength, the sintered dense alumina ceramics as well as the alumina single crystal were also applied to the artificial tooth roots. These tooth roots are fixed to the surrounding bone by mechanical interlocking between them, for example, through screw threads formed on the ceramics.[6] This type of fixation is, however, not always stable for long period.

3. Bone-Bonding Ceramics

The possibility for more stable fixation was shown by Hench et al in early 1970s. They proved that some glasses in the system Na_2O-CaO-SiO_2-P_2O_5 spontaneously bond to the living bones without any foreign body reaction.[7] These were the first man-made materials which had been found to bond to living tissues. They were named Bioglass® and successfully applied to artificial middle ear bones, alveolar ridge maintenance implants etc.[8]

Following their discovery, a glass-ceramic named Ceravital® precipitating an apatite and sintered hydroxyapatites were also found to bond to the living bone in 1973[9] and 1977[10], respectively. They were also applied to artificial middle ear bones. In addition, the latter was used as bone fillers in granular forms, as maxillofacial implants in porous forms and as artificial tooth roots in dense forms.[6] These bone-bonding materials are now called bioactive materials. Their mechanical strength are, however, not so high as that of human cortical bone. Therefore, their applications have been limited to unloaded or only a little loaded area.

4. High Strength Bioactive Ceramics

The natural bone is a composite in which an assembly of apatite small particles is effectively reinforced by the collagen fibers. Kokubo et al tried to prepare a similar composite by crystallization of a glass in 1982.[11] In this attempt, β-wollastonite ($CaO{\cdot}SiO_2$) consisting of a silicate chain structure was used as the reinforcing phase. A parent glass in the pseudoternary system $3CaO{\cdot}P_2O_5$-$CaO{\cdot}SiO_2$-$MaO{\cdot}CaO{\cdot}2SiO_2$ was once crushed into fine powders, pressed into a desired form and then subjected to a heat treatment.[12] As a result, a pore-free dense glass-ceramic where the oxyfluoroapatite ($Ca_{10}(PO_4)_6(O,F_2)$ and β-wollastonite in a form of rice grain 50 to 100 nm were homogeneously precipitated in a MgO-CaO-SiO_2 glassy matrix was obtained. The resultant glass-ceramic called A-W showed a bending strength about twice that of the sintered dense hydroxyapatite in practical uses and even higher than that of the human cortical bone in the air environment,[13] although the β-wollastonite did not take the fibrous form. In the body environment, it was expected that glass-ceramic A-W could withstand a continuous loading of bending stress of 65 MPa for over

10 years, where the parent glass, a glass-ceramic precipitating only the apatite and the sintered dense hydroxyapatite all might be broken within only 1 min., on the basis of the dependence of the bending strength upon stressing rate in a simulated body fluid with ion concentrations nearly equal to those of human blood plasma at 36.5°C.[14]

A rectangular specimen of glass-ceramic A-W implanted into a rabbit tibia was so tightly bonded to the surrounding bone that the fracture did not occur at the interface but within the bone, when a tensile stress was applied to their interface.[15] Granular specimens of the same glass-ceramic implanted into the same site were covered with a newly grown bone up to 90 % of their surfaces within 4 weeks, whereas the sintered hydroxyapatite only 60 % even after 16 weeks.[16]

Because of these mechanical and biological advantages, glass-ceramic A-W, which was named Cerabone® A-W commercially is already clinically used as iliac spacers, artificial vertebrae, intervertebral spacers, spinous process spacers etc., as shown in Fig. 2. When one of it substituted for a vertebra of a sheep, it was spontaneously bonded to the surrounding cancellous bone after a while, as shown in Fig. 3.[17] Until end of 1991, glass-ceramic A-W in the numbers given in Table 1 were subjected to clinical uses. Since approval from government for sale in May 1992, the numbers are increasing.

A summary of clinical uses of A-W glass ceramic untill end of 1991

Iliac crests prostheses	135 cases	
Vertebrae prostheses	76	(80 pieces in total)
Intervertebral spacer	6	(8 pieces in total)
Spinous process spacer	20	(80 pieces in total)
Granules as the bone defect fillers	32	

(Personal communication by Prof. T. Yamamuro, Kyoto University)

Even this glass-ceramic, however, can not replace highly loaded bones such as femoral bones, since its fracture toughness is not sufficiently high while the elastic modulus is not sufficiently low. Berger et al prepared a glass-ceramic named Ilmaplant® L1, which also precipitated the apatite and wollastonite, by crystallization of a bulk glass.[18] Vogel et al prepared a glass-ceramic named Bioverit®, which precipitated the apatite and phologophite.[19] Their mechanical strengths are, however, lower than that of glass-ceramic A-W.

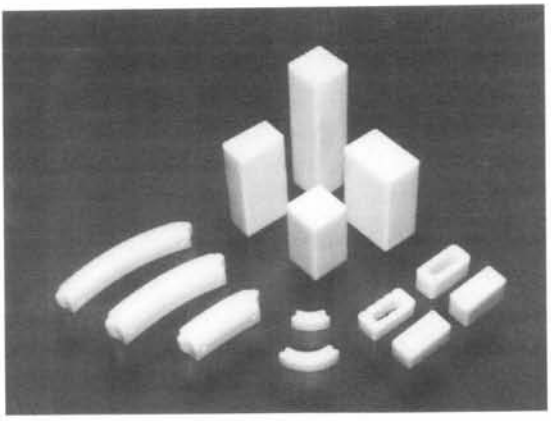

Fig. 2 Ilica spacers (left), artificial vertebrae (middle top) and interbertebral spacers (middle bottom) and spinous process spacers (right) of glass-ceramic A-W.

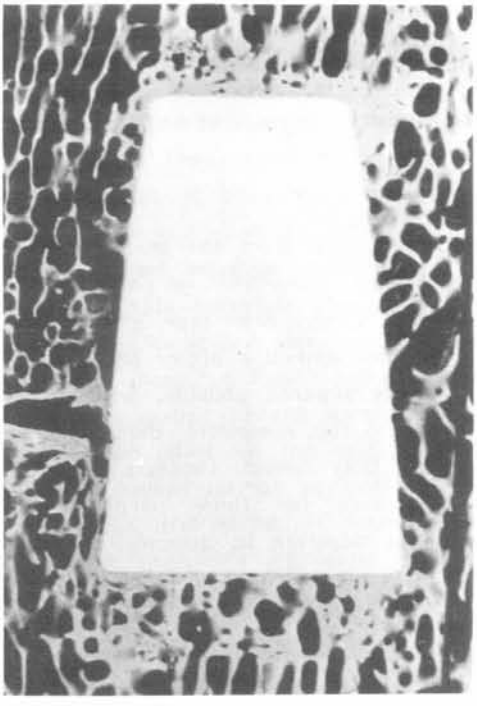

Fig. 3 Glass-ceramic A-W which substituted for a vertebra of a sheep and bonded to the surrounding cancellous bone. (contact radiomicrograph)

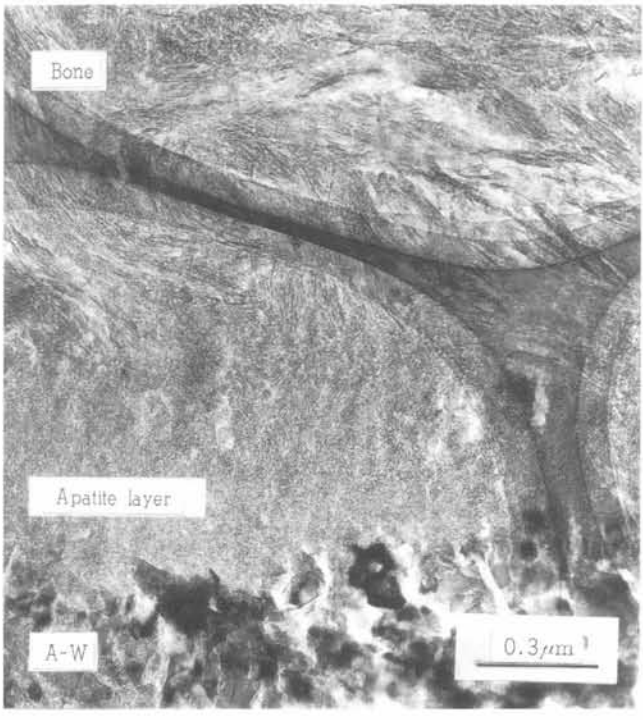

Fig. 4 Transmission electron micrograph of the interface of glass-ceramic A-W and rat tibia.

In order to increase further more the mechanical strength, some bioactive ceramics were reinforced with fibers[20,21] or particles of metals[22] or particles of ceramics.[23-25] Among them, A-W type glass-ceramic reinforced with 30 vol.% of the zirconia particles showed a higher bending strength than that of the high density and high purity sintered alumina, without giving adverse effect on the bioactivity.[26] Even with this composite, the human femoral bones, however, can not be replaced. Only metal implants coated with plasma sprayed hydroxyapatite are now used for these purposes.[27] The bond of the hydroxyapatite to the metal substrate is, however, not stable for long period and elastic moduli of the metals are much higher than that of the human bone.[28]

5. Bioactive Materials Mechanically Analogous to Natural Bone

In order to obtain a bioactive material with the elastic modulus similar to that of the bone, Bonfield et al prepared a composite in which sintered hydroxyapatite particles are dispersed in a polyethylene matrix.[28] Its bioactivity was, however, not so high as the pure sintered hydroxyapatite. A different

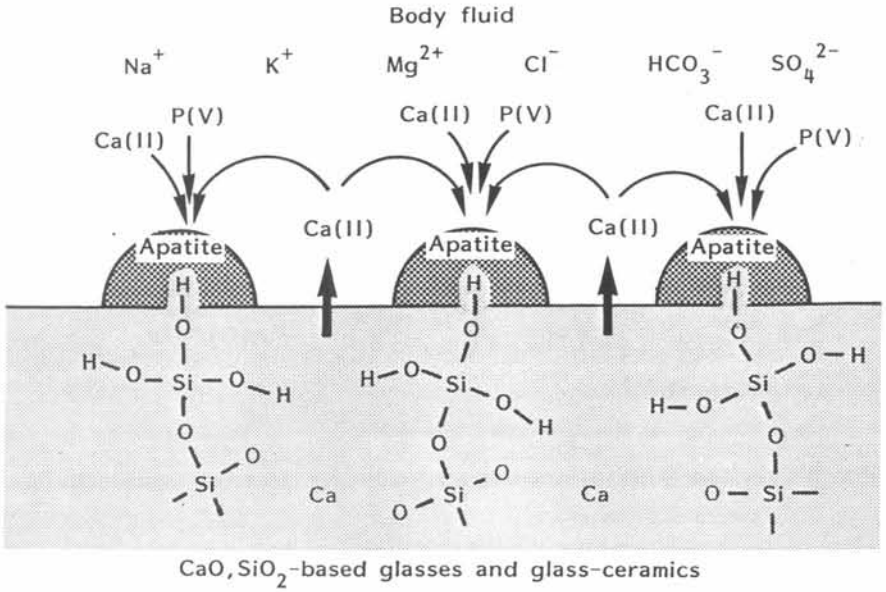

Fig. 5 Formation of biologically active bone-like apatite layer on the surfaces of CaO,SiO_2-based glasses and glass-ceramics.

approach is needed for obtaining a highly bioactive material with mechanical properties analogous to those of the natural bone. According to fundamental studies of bone-bonding mechanism of bioactive glasses and glass-ceramics, they bond to the living bone through a biologically active carbonate-containing bone-like apatite layer which is formed on their surfaces in the body, as shown in Fig. 4.[29-32] Formation of this bone-like apatite layer is initiated by the calcium ion dissolved from the glasses and glass-ceramics and the hydrated silica formed on their surfaces, as shown in Fig.5. The calcium ion increases the ionic activity product of the apatite in the surrounding body fluid, and the hydrated silica provides favorable sites for the apatite nucleation. As a result, the apatite nuclei are easily formed on the surfaces of CaO,SiO_2-based glasses and glass-ceramics. Once the apatite nuclei are formed, they spontaneously grow by consuming the calcium and phosphate ions from the surrounding body fluid, since the body fluid is already supersaturated even under the normal condition.[33-35]

On the basis of these findings, it is expected that even organic polymers could be coated with the bone-like apatite layer by the following biomimetic process at ordinary temperature and pressure. If a polymer substrate is placed on or in granular particles of a CaO, SiO_2-based glass soaked in the simulated

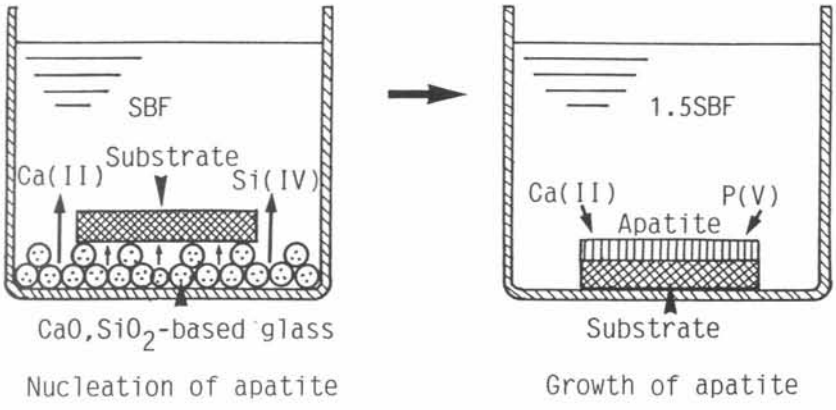

Fig. 6 Formation of bone-like apatite layer on polymer substrate by a biomimetic process.

body fluid (SBF) with ion concentrations nearly equal to those of the human blood plasma, as shown in Fig. 6, a large number of apatite nuclei could be formed on the substrate. Then, if the substrate is soaked in another solution supersaturated with respect to the apatite, for example, a solution with ion concentrations 1.5 times those of the simulated body fluid, the apatite nuclei could grow spontaneously on the substrate in situ, to form the bone-like apatite layer. Actually, dense and uniform layer of the bone-like apatite is formed on any kinds of polymer substrate, by this biomimetic process.[36,37] The thickness of the apatite layer increases with increasing soaking time in the second solution, and the rate of the growth of the apatite layer increases with increasing degree of the supersaturation and temperature of the second solution.[38] These formed apatite layer adheres fairly strongly to polyethyleneterephthalate and polyethersulfone.[39] It can be coated homogeneously even on single fibers and textiles, as shown in Fig. 7. A textile of polyethyleneterephthalate fine fibers coated with the bone-like apatite layers can be bent sharply without peeling off the apatite layer. It is expected that this type of polymer fibers or textile coated with the apatite layer could be constructed into a three dimensional structure with high bioactivity, as well as mechanical properties close to those of the natural bone not only in the strength but also in fracture toughness ad elastic modulus. In addition, polymer materials coated with the bone-like apatite layer could be useful even for repairing soft tissues, since they show high compatibility with these tissues as well as ductility. Applications of this type of composite to percutaneous access assist divices and artificial trachea are now successfully subjected to animal experiments.

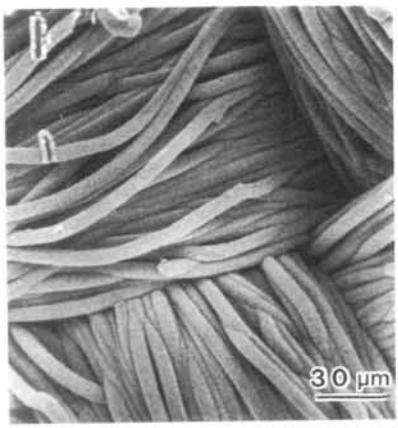

Fig. 7 A textile of polyehtyleneterephthalate fine fibers coated with the bone-like apatite layer 2 μm thick.

6. Self-Setting Bioactive Ceramics

On the basis of the bone-bonding mechanism, it is also expected that a self-setting bioactive ceramic also could be derived from the CaO, SiO_2-based glasses. Actually, a mixture of a $CaO\text{-}SiO_2\text{-}P_2O_5\text{-}CaF_2$ glass powder with an

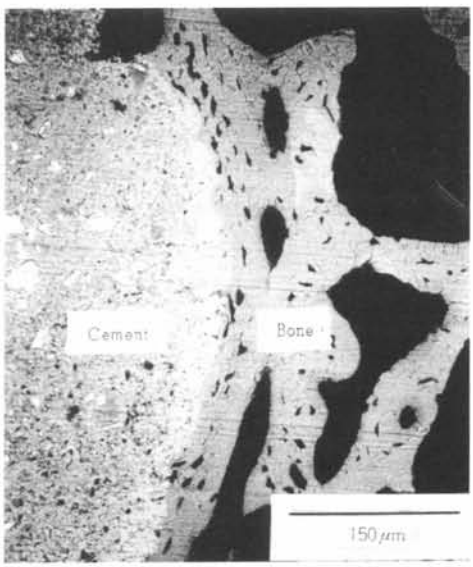

Fig. 8 Self-setting bioactive ceramic (cement) made of a CaO,SiO_2-based glass which bonded to the bone of rabbit tibia.

ammonium phosphate solution can be formed into any shapes within the first 3 min. sets at 4 min. [40] and bonds to the living bone within 4 weeks, as shown in Fig. 8.[41] The compressive strength of the solidified mixture increases with increasing time after implantation into the living body or immersion into the simulated body fluid, reaching 80 MPa, which is 3 or 4 times that of Portland cement, within 3 days.[40]

The fast set is attributed to the formation of the calcium ammonium phosphate monohydrate ($CaNH_4PO_4.H_2O$) at intergranular spaces of the glass powders and the successive hardening to the formation of the hydroxyapatite in place of the calcium ammonium phosphate.[40] If some medical drug is mixed with the glass powder, the drug can be released at a controlled rate at the site where the solidified mixture was implanted.[42] This type of self-setting bioactive ceramic is applicable to castable bioactive artificial bones, as well as to the drug delivery system. Attempts for developing similar self-setting bioactive ceramics have been made also by using crystalline calcium phosphates.[43]

7. Ferromagnetic Bioactive Glass-Ceramics

Ferromagnetic bioactive glass-ceramics also can be derived from the CaO, SiO_2-based glasses.[44] A FeO-Fe_2O_3-CaO-SiO_2-B_2O_3-P_2O_5 glass gives a glass-ceramic precipitating ferrimagnetic magnetite (Fe_3O_4) in a bioactive CaO, SiO_2-based matrix, when subjected to a heat treatment. The resultant glass-ceramic shows a ferromagnetism of a saturation magnetization of 32 emu/g and a coercive force of 120 Oe, as well as bioactivity.[45] When this type of glass-ceramic is implanted around tumor in granular forms, they bond together and also to the bone, to be fixed around the tumor, and then when the tumor is placed under an alternating magnetic field, the tumor is heated locally up to temperatures effective for cancer treatment i.e. around 43°C, by magnetic hysteresis loss.[46] For example, a bone tumor was transplanted to the intramedullary canal of rabbit tibia, 2 weeks later a pin 3 mm in diameter 5 cm long of the glass-ceramic was inserted into the tibia, and they subjected to an alternating magnetic field of 100 kHz up to 300 Oe for 50 min. It was confirmed 3 weeks later that the cancer cells in the canal were completely killed and the structure and function of the bone were recovered, as shown in Fig. 9.[47] This type of ferromagnetic bioactive glass-ceramic is useful as the thermoseeds for hyperthermia treatment of the cancer, especially for the deep seated cancer where other heating method can not be applied. A ferrimagnetic but not bioactive glass-ceramic containing lithium ferrite ($LiFe_5O_8$) was early developed by Luderer et al[48] for the thermoseeds.

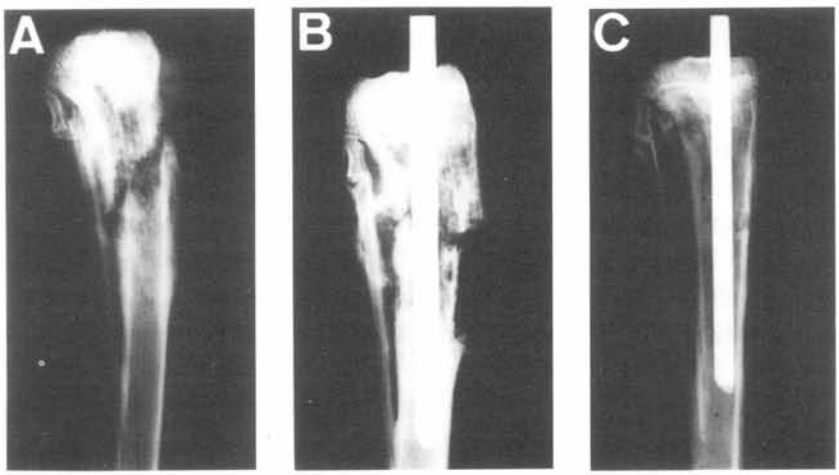

Fig. 9 Effect of hyperthermia treatment with ferromagnetic bioactive glass-cermic on bone tumor. A: No treatment B: Only pinning C: Pinning and hyperthermia treatment

8. Radioactive Glasses

Non-bioactive but chemically stable glass is also useful for cancer treatment. Y_2O_3-Al_2O_3-SiO_2 glasses show high chemical durability. The yttrium in the glasses is not radioactive during the melting and forming process, but activated to β-emitter with a half-life time of 64.1 h by neutron bombardment. When microspheres 20 to 30 μm in size of this glass activated are injected to the liver tumor through artery, they give large local radiation dose of the short-ranged, highly ionizing β-ray to the tumors, with little irradiation to neighboring organs.[49] This type of glass is already successfully subjected to clinical trials of the cancer treatment.

9. Glass-Ceramics for Dental Crown

Glass melt can be easily formed into various shapes by casting method. Thus formed glass can be converted into glass-ceramic with a high mechanical strength, as well as color and translucency similar to those of the natural teeth by a heat treatment, without giving appreciable change in the shape and size. Therefore, various kinds of glass-ceramics have been developed for the dental crown[33], and some of them are already clinically used.[50]

10. Carbons

Isotropic carbons deposited at relatively low temperature show exceptionally high resistance against the thrombosis, as well as the wear and fatigue.

Therefore, most of the artificial heart valve is now made of this type of carbon.[51]

11. Conclusion

Now, it is apparent that ceramics can play an unique and important role in repairing not only damaged hard tissues but also damaged soft tissues. Ceramics can not only substitute for the damaged tissues, but also destroy them in situ without excising, and promote their self-repairing activities by electromagnetic effects. Fundamental understanding of reaction of ceramics with living tissues has also largely progressed. This provides us not only method for developing new kinds of ceramics for biomedical applications, but also new techniques for preparing ceramics with highly controlled structures for various applications through biomimetic process at ordinary temperature and pressure. Because of these potential of ceramics, international symposiums on ceramic in medicine and on synthesis of ceramics by utilizing biological processes are now frequently held.

There is, however, some problems to be solved for ceramics to continue to grow steadily in these fields. Most of the participants at the symposiums on ceramics in medicine are medical scientists but not ceramic scientists. If this situation could not be changed immediately, ceramics might be disappeared from biomedical fields soon or later. Without development of new ceramics by ceramic scientists, medical doctors can not develop new medical treatments using ceramics. At that time, we, all of whom are candidates of patient, could not enjoy healthy life which ceramics could provide us. Various social and economical conditions must to be changed to solve this problem. Education of ceramics also must be changed. At least, textbooks of ceramics should spare one chapter for biological and medical properties of ceramics.

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