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Bioactive Materials

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Abstract: Bioactive materials, including bioactive glasses, bioactive glass-ceramics, bioactive calcium phosphate ceramics and bioactive composites and coatings, bond to living tissues. The implant–tissue interfacial reactions and bonding mechanisms of the different bioactive materials are summarized. There are two types of bioactivities, osteoproductive bioactivity and osteoconductive bioactivity, due to different rates and mechanisms of implant–tissue interactions. To optimize the biochemical compatibility and biomechanical compatibility of the materials, two directions are proposed: (1) structural tailoring of bioactive composites and coatings and (2) molecular tailoring of surface chemistry. © 1996 Elsevier Science Limited and Techna S.r.l.

1 INTRODUCTION

1.1 Tissue attachment of biomaterials

The mechanism of tissue attachment of an implant is directly related to the tissue response at the implant interface.[1] No material implanted in living tissues is inert; all materials elicit a response from the host tissue. According to the different types of implant–tissue attachment, biomaterials are classified into four types, which are summarized in Table 1 with examples.[2] The tissue response to a biologically inactive, nearly inert implant is formation of a non-adherent fibrous capsule. The thickness of the fibrous layer depends on many factors, such as the conditions of the implant, the conditions of the host tissue, the conditions of motion and fit at the interface and the mechanical load. A chemically stable material like alumina elicits a very thin capsule under an optimal mechanical fit.[3] More chemically reactive metallic implants elicit thicker interfacial fibrous layers. Because the interface is not chemically or biologically bonded, relative movement can occur, called micromotion. This movement results in progressive development of the non-adherent fibrous capsule and eventually leads to deterioration in function of the implant or the host tissue at the interface or both. Porous biomaterials provide interfacial fixation by ingrowth of tissue into pores on the surface or throughout the implant. This attachment is called "Biological Fixation". It is capable of withstanding more complex stress states than dense nearly inert implants which achieve only "morphological fixation". Good biological fixation requires pores that are greater than 100–150μm in diameter to provide a blood supply to the host tissues.[3] Resorbable implants are designed to degrade gradually with time and be replaced with natural host tissues. For example, resorbable sutures composed of poly(lactic acid)–poly(glycolic acid) are metabolized to carbon dioxide and water. Tricalcium phosphate ceramics degrade to calcium and phosphate salts. Because large quantities of material must be handled by cells, the constituents of a resorbable implant must be metabolically acceptable. Another requirement for a resorbable implant is that the resorption rate must be matched to the repair rates of body tissues.[4] Bioactive implants offer another approach to achieve interfacial attachment. When a bioactive material is implanted in the body, a series of biophysical and biochemical reactions occur at the implant–tissue interface. These reactions eventually result in a

Table 1. Types of tissue attachment of biomaterials

Type of implant	Type of attachment	Example
1) Nearly inert	Mechanical interlock (morphological fixation)	Metals, Alumina, Zirconia, Polyethylene(PE)
2) Porous	Ingrowth of tissues into pores (biological fixation)	Hydroxyapatite (HA), HA coated porous metals
3) Bioactive	Interfacial bonding with tissues (bioactive fixation)	Bioactive glasses, HA, Bioactive glass-ceramics
4) Resorbable	Replacement with tissues	Tricalcium phosphate, Polylactic acid (PLA)

mechanically strong chemical interfacial bonding.[1,5] This attachment is called "Bioactive Fixation", which is discussed in the following sections.

1.2 General theory of biomaterials

The surface chemistry of implants needs to be optimized to meet the requirements of aged, diseased and damaged tissues. Biocompatibility, or tissue tolerance, is not enough. A general theory of biomaterials was expressed by Hench and Ethridge in 1982 as:[1]

(a) An ideal implant material performs as if it were equivalent to the host tissue.
(b) Axiom 1. The tissue at the interface should be equivalent to the normal host tissue.
(c) Axiom 2. The response of the material to physical stimuli should be like that of the tissue it replaces.

These axioms are interdependent. A stable interfacial bond between tissue and implant must be achieved in order to obtain an equivalent physical response, and controlled physical stimuli is necessary for a stable interface to be produced. This general theory requires that a biomaterial have both biochemical compatibility and biomechanical compatibility. So, besides bioactivity, a match in physical and mechanical properties is also essential for an implant to replace bone. For example, a high Young's modulus of an implant results in its carrying nearly all the load and leads to stress shielding of bone. Bone must be loaded in tension to remain healthy. Stress shielded bone will undergo a biological change that leads to bone resorption, and the interface between a stress shielded bone and an implant will deteriorate as the bone structure is weakened.

One of the great challenges facing the field of biomaterials is the rapidly growing use of implants combined with the increasing life expectancy of patients. An increasing fraction of patients will outlive the expected lifetime of their implants. A new generation of implant materials and prostheses designs are needed with a lifetime of 20–40 years, double the lifetime of many current devices. Because of this reason, the focus of research and understanding of long-term performance of prosthetic devices must be on creating an implant–tissue interface which is simultaneously histologically and biomechanically stable.

2 BIOACTIVITY

In the early 1970s, bioceramics began to be used in certain implant applications, which depended on the fact that a smooth oxide ceramic surface, especially Al_2O_3, elicited very little tissue reaction and provided good wear characteristics for a bearing surface. In 1969, the concept of a bioactive material was discovered.[6] Since then, the field of ceramics has expanded enormously to include many new compositions of glasses, glass-ceramics and ceramics.[2,7] The concept of bioactivity was defined as: "A bioactive material is one that elicits a specific biological response at the interface of the material which results in the formation of a bond between the tissues and the material".[6] It is intermediate between resorbable and bioinert.[1,5,7] A bioactive material creates an environment compatible with osteogenesis (bone growth), with the mineralizing interface developing as a natural bonding junction between living and non-living materials. This concept has now been expanded to include a large number of bioactive materials with a wide range of rates of bonding and thickness of interfacial bonding layers. They include bioactive glasses such as Bioglass®, bioactive glass-ceramics such as Ceravital®, A/W glass-ceramics and machineable glass-ceramics, dense calcium phosphate ceramics such as synthetic hydroxyapatite (HA), bioactive composites such as PE–HA mixtures, and a series of bioactive coating materials. For the various bioactive materials, the mechanism of bonding, the time dependence of bonding, the strength of the bonding, the thickness of bonding zone are different. The rate of development of the interfacial bond can be referred to as the level of bioactivity. Relative bioactivity and time dependence of formation of interfacial bone bonding for various bioceramics are shown in Fig. 1.[2,8]

The level of bioactivity of a specific material can be related to the time for more than 50% of the interface to be bonded. An index of bioactivity introduced by Hench[5] as: $I_B = 100/t_{0.5bb}$, where

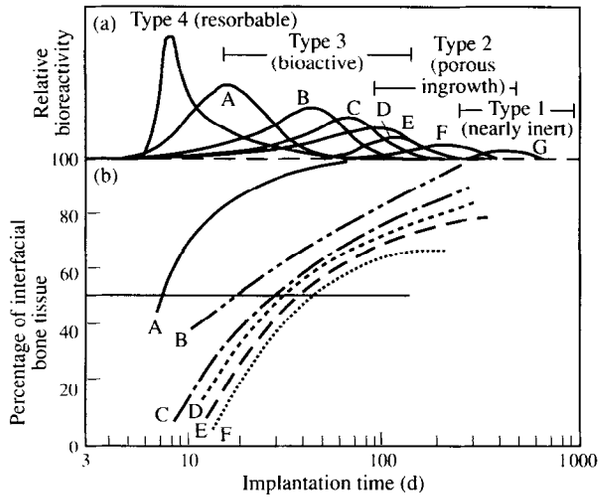

Fig. 1. Bioactivity spectrum for various bioceramic implants: (a) relative rate of bioactivity and (b) time dependence of formation of bone bonding at an implant interface. [(A) 45S5 Bioglass®, (B) Mina13 Ceravital®, (C) 55S4.3 Bioglass®, (D) A/W glass-ceramic, (E) HA, (F) KGy213 Ceravital®.]

$t_{0.5bb}$ is the time for more than 50% of the implant interface to be bonded to bone. All the *in vitro* and *in vivo* test results show that the only common characteristic of the known bioactive implant materials is that a layer of biologically active hydroxyl carbonate apatite forms on the implant surface.

However, the large difference in rate of bone bonding to bioactive implants indicates that different biochemical factors are occurring at the implant–tissue interface. In 1994, a new hypothesis was proposed,[8] in which bioactive materials are classified into two types:

1. Class A, osteoproductive materials. Osteoproduction has been defined by Wilson as, "The process whereby a bioactive surface is colonized by osteogenic stem cells free in the defect environment as a result of surgical intervention."[9] Class A bioactivity occurs when a material elicits both an *intracellular* and an *extracellular* response at its interface. Class A bioactive glasses can bond with *both* bone and soft tissue.
2. Class B, osteoconductive materials. The osteoconductive implant simply provides a biocompatible interface along which bone migrates. Osteoconductive bioactivity occurs when a material elicits only an *extracellular* response at its interface.[4]

Of the current bioactive materials, only a few bioactive glasses with high I_B have osteoproductive bioactivity (Fig. 1). Synthetic hydroxyapatite (HA) implants are osteoconductive; i.e. they have class B bioactivity. 45S5 Bioglass®, a class A bioactive material, is both osteoproductive and osteoconductive.

3 BIOACTIVE CERAMICS

3.1 Bioactive glasses and glass-ceramics

The base components in most bioactive glasses and glass-ceramics, made by traditional high temperature melting, casting and sintering, are SiO_2, Na_2O, CaO and P_2O_5. The first and well-studied composition is 45S5 Bioglass®, which contains 45% SiO_2, 24.5% Na_2O, 24.5% CaO and 6% P_2O_5, in weight percent. The composition and some mechanical properties of several typical bioactive glasses are given in Table 2.

A series of glasses in this four-component system with a constant 6 wt% P_2O_5 were studied. The compositional dependence of the bioactive bonding-boundary for this system is shown in Fig. 2.[2,8]

In the region A the glasses are bioactive and bond to bone. Glasses in region B behave as nearly

Table 2. Composition (wt%) and mechanical properties of bioactive glasses

Component	45S5 Bioglass®	45S5.4F Bioglass®	45B15S5 Bioglass®	52S4.6 Bioglass®	55S4.3 Bioglass®
SiO_2	45	45	30	52	55
P_2O_5	6	6	6	6	6
CaO	24.5	14.7	24.5	21	19.5
Na_2O	24.5	24.5	24.5	21	19.5
CaF_2		9.8			
B_2O_3			15		
Class	A	A	A	A	B
BS (MPa)	40–60				
E (GPa)	30–50				
Reference	1	6	10	11	11

BS: Bending Strength, E: Young's Modulus.

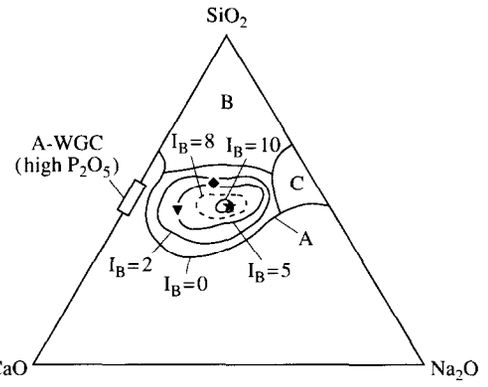

Fig. 2. Compositional dependence (in weight percent) of bone bonding and soft-tissue bonding of bioactive glasses and glass-ceramics. All compositions in region A have a constant 6% of P_2O_5. A/W glass-ceramic has a higher P_2O_5 content. Region E (soft-tissue bonding) is inside the dashed line where $I_B > 8$. [(⋆) 45S5 Bioglass®, (▼) Ceravital®, (◆) 55S4.3 Bioglass®.]

inert materials and result in a fibrous capsule at the implant–tissue interface. Glasses in region C are resorbed within 10–30 days in tissue. Compositions in region D are not technically practical and have not been implanted. In the middle of area A, a smaller region is indicated (in broken line), within which the collagenous constituent of soft tissues can strongly adhere to the bioactive glasses. Iso I_B lines showing compositions of equivalent index of bioactivity are shown in Fig. 2.

The low strength of a monophase bioactive glass restricts its clinical application to non-load bearing situations. A way to attempt to solve this problem is to prepare a glass-ceramic by a process of crystallization of glass.[7,12,13] Several kinds of bioactive glass-ceramics have been developed, including bioactive A/W glass-ceramic, Ceravital glass-ceramics and machineable glass-ceramics. The compositions and mechanical properties of these glass-ceramics are given in Tables 3 and 4. The mechanical strength of the glass-ceramics has been improved considerably. These glass-ceramics also show bioactivity by bonding to bone.[14–16] Machineable glass-ceramics have high levels of machineability because of a mica phase crystallized during heat treating.[17]

4 MECHANISM OF BIOACTIVE BONDING

A common characteristic of bioactive materials is a time-dependent, kinetic modification of the implant surface that occurs upon implantation. Figure 3 summarizes the sequence of eleven reactions which occur on the surface of a bioactive glass as a bond with bone is formed.[2] The first five reaction stages that occur on the glass side of the interface do not depend on the presence of tissues. They occur in distilled water, tris-buffer solutions or simulated body fluids (SBF), and have been well studied using Fourier transform infrared (FTIR) spectroscopy,[18] Auger electron spectroscopy and electron microprobe analysis.[19] These reactions result in a hydroxy carbonate apatite (HCA) crystal layer forming on the implant surface. Stages 6–11 are necessary for the implant to bond to tissues. Two kinds of interactions between the implant and tissue will happen:

Table 3. Composition (wt%) and mechanical properties of A/W and Ceravital® glass-ceramics

Component	A/W Glass-ceramic®	KG Cera Ceravital®	Mina 13 Ceravital®	KGy213 Ceravital®	M8/1 Ceravital®
SiO_2	34.2	46.2	46	38	50
$Ca(PO_3)_2$		25.5	16	13.5	7.1
CaO	44.9	20.0	33	31	
P_2O_5	16.3				
Na_2O		4.8		4	5
MgO	04.6	2.9	5		
CaF_2	0.5				
K_2O		0.4			
Al_2O_3				7	1.5
Ta_2O_5				5.5	
TiO_2				1	
B_2O_3					4
$Al(PO_3)_3$					2.4
SrO					20
La_2O_3					6
Gd_2O3					4
BS (Mpa)	215				
E (Gpa)	35			70–88	
Reference	12	13	13	13	13

BS: Bending Strength, E: Young's Modulus.

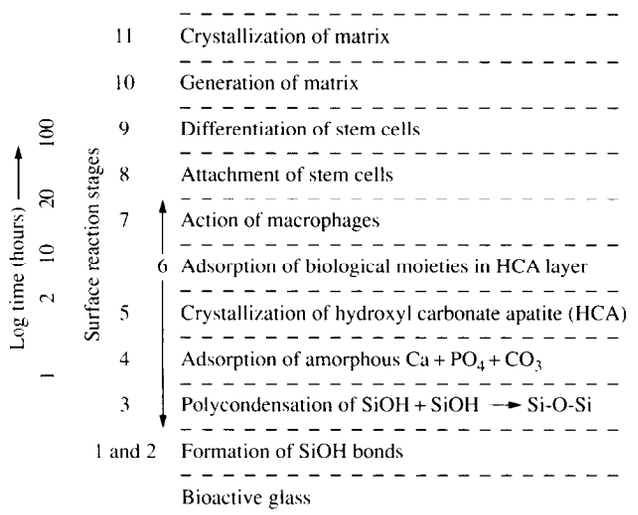

Fig. 3. Sequence of interfacial reactions involved in forming a bond between tissue and bioactive glasses.

1. Extracellular interaction, which is determined by the material's surface features. Surface nanometre scale porosity and negatively charged silonals play an important role in the material surface adsorption of proteins and collagen. Different surfaces have different protein adsorption properties. For example, a surface having clot-lysing properties can preferentially adsorb plasminogen (the principal proenzyme of the fibrinolytic pathway) from plasma. Woodhouse *et al.* showed that lysine-derivatized silica glass adsorbed more plasminogen relative to fibrinogen and the adsorbed plasminogen appeared to be in a conformation that was more readily activated to plasmin.[20] Vroman proposed that albumin, IgG, fibrinogen–fibrionectin, and Hageman factor-HMWK were sequentially adsorbed on the material surface, and the sequence occurred more rapidly on negatively charged surfaces. The negatively charged surfaces can also promote the activation of the Hageman factor by rendering the adsorbed protein more susceptible to limited proteolysis.[21] Protein adsorption is followed by coagulation and activation of the complement system and cellular adhesion. The interactions between osteoblast receptors and the corresponding protein ligands on the surface contribute to the cellular adhesion. Another important consequence of protein adsorption is transforming the zymogens into active enzymes.[22,23] On the implant surface, the adsorbed proteins, such as bone growth factors and activated enzymes, have a direct effect on cell differentiation and proliferation. Material surface topographic configurations also have a large effect on cellular behaviour and tissue response. Green *et al.* showed that adsorbed cells on 2 and 5μm arrays had increased rates of proliferation and cell density.[24] This result means that the HCA crystallinity on the bioactive material surface may have an effect on stem cell differentiation. On the surface of bioactive ceramics, osteoblast proliferation is favoured over fibroblast proliferation[1,25] because of a series of chemically specific protein adsorption and cell membrane-attachments, which are still under investigation.
2. Intracellular interaction, which may be caused by the soluble silicon release from glass surface with highest I_B values. Studies by Keeting *et al.* showed that soluble silicon was a potent

Table 4. Composition (wt%) and mechanical properties of machineable bioactive glass-ceramics

Component	Biovert I	Biovert II	Biovert III
SiO_2	29.5–50	43–50	
CaO	13–28	0.1–3	13–19
P_2O_5	8–18	0.1–5	45–55
Al_2O_3	0–19.5	26–30	6–18
Na_2O			11–18
Na_2O/K_2O	5.5–9.5	7–10.5	
MgO	6–28	11–25	
F	2.5–7	3.3–4.8	
Cl	0.01–0.6		
TiO_2	additions		
$MeO/Me_2O_5/MeO_2$ (MnO, CoO, NiO, FeO, Fe_2O_3, Cr_2O_3, ZrO_2)			1.5–10
BS (MPa)	140–180	90–140	60–90
E (GPa)	70–88	70	45
Reference	14	14	14

BS: Bending Strength, *E*: Young's Modulus.

mitogen for human osteoblast-like cells, increased DNA synthesis and enhanced alkaline phosphatase activity and osteocalcin release.[26] Vrouwenvelder *et al.* demonstrated that osteoblast cells divide more rapidly on bioactive glass substrates than they do on synthetic HA.[27] Carlisle's early studies on chicks and rats showed that bone grew rapidly in the presence of silicon, whereas a silicon deficient environment retarded bone growth.[28] All these results indicate that soluble silicon plays an important role in tissue repair and osteogenesis. Another characteristic of Class A bioactive glass is its soft-tissue bonding property. Class B bioactive materials, such as HA or glasses with a low soluble silicon release, can not form stable bonding with soft tissues. Soluble silicon may also elicit an intracellular effect on collagen or polysaccharide cross linking, which leads to the tight bonding between the mineral apatite layer and collagen fibres. Further investigations are needed to determine the biological pathways of soluble silicon and the metabolic functions involved in osteogenesis.

The time scale for the surface reactions of a glass with a high I_B is shown in Fig. 3. The surface reaction speed is mainly controlled by the material composition. For glasses with up to about 53 mole percent SiO_2, HCA crystallization occurs very rapidly on the glass surface, within 2 h. These compositions develop a rapid bond with bone and also form an adherent, interdigitating collagen bond with soft tissues. Glasses with SiO_2 content between 53 and 58 mole percent SiO_2 require 2–3 days to form the HCA crystalline layer. Compositions with $>60\%$ SiO_2 do not form a crystalline HCA layer even after 4 weeks in SBF.[29] Fluoride additions can promote the formation of the HCA layer while reducing the rate of network dissolution of the bioactive glass and affect the A–C boundary in Fig. 2. Substitutions of MgO, K_2O and B_2O_3 in the glass have little effect on bone bonding.[2] However, Al_2O_3 can inhibit bone bonding, as can other multivalent cations such as Ta_2O_5, TiO_2, Sb_2O_3 and ZrO_2.[7,16] This negative effect of ions such as Al^{3+} on bone bonding is attributed to an increased resistance to ion exchange surface reactions, to the precipitation of the multivalent ions as oxides, hydroxides or carbonates, and to the shift of isoelectric point of the surface from negative to positive at physiological pH.[30,31]

5 CALCIUM PHOSPHATE CERAMICS

Since Levitt *et al.* described a method of preparing an apatite ceramic from mineral fluorapatite and suggested the possible use of this apatite ceramic in medical applications in 1969,[32] calcium phosphate ceramics have been widely studied for clinical uses. Calcium phosphate ceramics can be prepared using several different methods, such as precipitation methods, hydrolysis method, solid-state reaction, hydrothermal reactions and the sol–gel method.[33–36] Only two calcium phosphates are stable in contact with aqueous media. At pH < 4.2 the stable phase is $CaHPO_4 \cdot 2H_2O$ (DCP), whereas at pH > 4.3 the stable phase is $Ca_{10}(PO_4)_6(OH)_2$ (hydroxyapatite, HA). Consequently, all the high-temperature calcium phosphate phases interact with water or body fluids at 37°C to form HA. The induction time to form crystallized-carbonated apatite increases as follows: CDHA (Ca-deficient HA) < nwCHA (not well crystallized HA) < wcHA (well crystallized HA) < I-HA (coralline HA) < β-TCP (β-tricalcium phosphate) < I-CC (calcium carbonate marine coral) < I-β-CP (β-calcium pyrophosphate).[37] The two calcium phosphate ceramics widely used in clinical application are B-TCP and HA. TCP is a resorbable temporary bone space filler material. When implanted, TCP will interact with body fluids to form HA as follows:

$$4Ca_3(PO_4)_2\ (s) + 2H_2O \rightarrow Ca_{10}(PO_4)_6(OH)_2\ (\text{surface}) + 2Ca^{2+} + 2HPO_4^{2-}$$

This reaction will decrease the pH of the local solution and further increases the solubility of TCP. Theoretically, resorbable TCP is an ideal implant material. After implantation, TCP will degrade with time and be replaced with natural tissues. It leads to the regeneration of tissues instead of their replacement and so solves the problem of interfacial stability. However, in clinical applications, some limitations restrict the use of resorbable TCP:

1. The mechanical performance of an implant must match the repair rate of body tissues. So, the degradation speed of the implant must be controlled very well.
2. Large quantities of implant must be handled by cells so the constituents of a resorbable implant must be metabolically acceptable. TCP implants dissolve by grain-boundary degradation. The released grains may cause a potential metabolic problem because of their size.[7]

The mineral phase of calcified tissues (enamel, dentine, bone) is biological apatite, which is HCA. A comprehensive understanding of the differences

between the biological apatite and pure synthetic HA is important to the manufacture, design, and use as an implant. These differences are:

1. Biological apatites are usually calcium-deficient and are always carbonate substituted. Biological apatite contains 3.2–5.8wt% carbonate. Consequently, biological apatites should be referred to as carbonate apatite.[38,39] Biological apatites also contain other minor elements and trace elements, as described below: $(Ca,M)_{10}(PO_4, CO_3, Y)_6(OH, F, Cl)_2$, where M represents Mg, Na, K and trace elements Sr, Pb, Ba, etc. Y represents acid phosphate, HPO_4, sulfates, borates, vanadates, etc. These elements will change the lattice parameters and the crystal properties of apatite.[35,40]
2. There is a large microstructural difference between biological HCA apatite and synthetic HA ceramic. For example, an enamel HA grain has a preferential growth along the (001) direction with a length and diameter ratio of 3–5 and there are always lattice defects at the grain boundary. In contrast, the synthetic HA ceramic is much more isotropic with a much larger grain size. Enamel and cortical bone have a high strength because of this unique microstructure.[40,41]
3. Biological apatite also contains organic materials. The content of organic phases in enamel and bone are about 1.0 wt% and 25 wt%, respectively. The organic phase exists at the grain-boundaries and has a large influence on the physical–chemical and biological properties of the apatite. Bone must be regarded as a composite of organic substance, primarily collagen, and an inorganic substance, primarily HCA.[40,41] Synthetic HA ceramics are not equivalent to biological apatite.

The bonding mechanisms of synthetic HA implants is different from those described for bioactive glasses. There are two models for bone bonding to implanted synthetic HA ceramics.

5.1 Dissolution/precipitation model

An acid condition will be produced at the implant area immediately after implantation. The acid condition results from cellular activity and the enzymes produced, and is different for various implantation conditions.[42] This acidic condition initiates partial dissolution of HA, causing release of Ca^{2+}, HPO_4^{2-} and PO_4^{3-}, and increases the supersaturation of the micro-environment with respect to the calcium phosphate phase. The surface characteristics of HA will be changed with this dissolution and a layer of carbonate–apatite can precipitate on this surface through seeded growth on HA crystals.[43] Formation of a biological HCA layer, however, is very slow with its rate controlled by the crystallinity of the synthetic HA and its dissolution kinetics.

5.2 Epitaxial growth model

The dissolution of HA is also governed by the chemical composition, crystal structure, microporosity, and neck dissolution rate of the materials. Under some implantation conditions, well-crystallized HA with a low dissolution rate will not experience morphologically discernible signs of dissolution. Bone tissue components will bond directly to HA crystals through epitaxial growth.[44]

A study by de Bruijn *et al.* showed that a layer of 0.1–1.1 μm globular accretions and proteinaceous material appeared on the degrading hydroxyapatite surface and fused to form a cement-like matrix, to which collagen fibres were attached. The latter change in surface topography may enhance bonding of the cement-like matrix to an hydroxyapatite implant.[45]

6 BIOACTIVE COMPOSITES AND COATINGS

All of the bioactive bioglasses, glasses-ceramics and calcium phosphate ceramics mentioned above form a mechanically strong interfacial bond with bone. The strength of the bond is generally equivalent to or greater than the strength of the host bone, depending on test conditions. Thus, all of these materials have excellent biochemical compatibility (bioactivity). However, bioactive ceramics have a flexural strength, strain-to-failure, and fracture toughness that is less than bone and an elastic moduli that is greater than bone. It means that most bioactive materials have a less than optimal biomechanical compatibility when used in load-bearing applications. An approach to solving this problem is structural tailoring of bioactive composites or coatings.

6.1 Bioactive composites

Depending on the goal, bioactive composites can be divided into two groups:

1. Use of a high fracture tough phase to reinforce the bioactive glasses or glass-ceramics. These reinforcing phases involve metal fibres or tough ceramic particles (Table 5). The

Table 5. Bioactive composite with a fracture tough reinforcing phase

Matrix	Reinforcing phase	Reference
Bioglass®	Stainless steel fibre	46,47
Bioglass®	Titanium fibre	46,47
HA	Fe–Cr–Al fibre	48
HA	ZrO_2 (Y_2O_3) particles	49
HA	TiO_2 particles	50
A/W glass-ceramic	ZrO_2 (Y_2O_3) particles	51
Ceravital glass-ceramic	Ti particles	52

Table 6. Bioactive composite of polymer and bioceramic

Matrix	Reinforcing phase	Reference
Polyethylene	HA	53
Polymer	Phosphate powder	54,55
Poly(methyl methacrylate)	Phosphate–silicate–apatite glass fibre	55
Collagen	HA	55
Polyethylene	Bioglass®	56
Polysulfone	Bioglass®	57

reinforced bioactive glasses and glass-ceramics are improved in both bending strength and fracture toughness. For example, Bioglass® reinforced with stainless steel fibres (60 vol%) has an enhanced bending strength up to 340 MPa. For an HA/$ZrO_2(Y_2O_3)$ composite, there is a strength enhancement to 450 MPa in bending with a fracture toughness of 3.0 MPa · $m^{1/2}$, which is much better than those of sintered dense HA ceramic (115–200 MPa and 1.0 MPa · $m^{1/2}$, respectively). The strongest of the bioactive composites is composed of A/W glass-ceramic containing a dispersion of tetragonal zirconia. A bending strength value of 703 MPa and K_{IC} value of 4 MPa · $m^{1/2}$ can be obtained with a volume fraction of 0.5 zirconia. All these composite materials are bone bonding in *in vivo* tests and form a layer of HCA on the surface under *in vitro* test conditions. Often the rate of reaction is very low, however. An additional disadvantage of these composites is that they all have elastic moduli much greater than bone and thus give rise to stress shielding of bone.

2. The second group of composites uses bioactive glass or ceramic particles or fibres to reinforce an elastically compliant and biocompatible polymer matrix, as pioneered by Bonfield *et al.*[53] The goal is a bioactive composite with a Young's modulus that matches that of bone (7–25 GPa depending on age, location and direction of measurement). The organic matrix includes polymers such as polyethylene, poly(methyl methacrylate), polysulfone, or collagen. The bioactive phases are calcium phosphates, bioactive glasses or HA powders and glass fibres (Table 6).

Polymer–bioactive ceramic composites solve the problem of stress shielding. For example, the Young's modulus of PE/HA composite is increased from 1 to 8 GPa as the volume fraction of HA increases from 0 to 0.5.[53] At 0.45 volume fraction of HA, the K_{IC} value is 2.9 MPa · $m^{1/2}$ and tensile strength remains within the range of 22–26 MPa. Thus, the mechanical properties of PE–HA composite are close to those of bone (Fig. 4). A Polyethylene–Bioglass® bioactive composite (PE/BG)

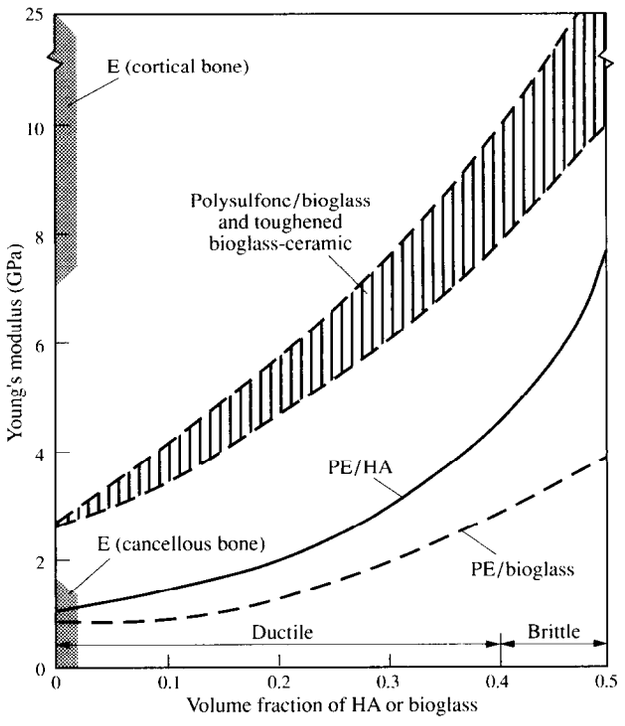

Fig. 4. Effect of volume fraction of bioactive phase (HA and BG) on Young's modulus (E) of reinforced polyethylene composites (PE/HA and PE/BG) and polysulfone composite (PS/BG), in comparison to cortical bone and cancellous bone.

Table 7. Bioactive coatings

Substrate	Coating	Reference
316L stainless steel	Bioglass® or HA	58,59
Co–Cr alloy	Bioglass® or HA	59,60
Ti–6Al–4V alloy	TCP, HA or Bioglass®	59,61,62
Ti–6Al–4V alloy + Ti powder or porous beads	HA, TCP	59
Alumina	45S5 Bioglass®	63

has mechanical properties similar to cancellous bone or soft tissues (Fig. 4). A polysulfone–Bioglass composite (PS–BG) shows a similar dependence on volume fraction of the dispersed glass phase (Fig. 4). The elastic modulus and strain to failure of the PS–BG composite is an excellent match with the mechanical properties of cortical bone.

Bioactive composites have the necessary combination of bioactivity and mechanical properties to be an ideal bone replacement material. However, long-term durability tests and fatigue tests in load-bearing physiologic environments are required before it is proven that these materials will provide 20–40 years lifetime.

6.2 Bioactive coating

Another approach to solving the mechanical limitations of bioactive glasses and ceramics for load-bearing applications is to apply the material as a coating on a mechanically tough substrate. Metals and medical grade alumina are commonly used as substrates, as shown in Table 7. Various techniques are available to deposit calcium phosphate coatings on metal implants, including hot isostatic pressing, plasma or flame spraying, ion-beam sputter deposition, frit enamelling, electrophoretic deposition, sol–gel deposition and radio-frequency (RF) magnetron sputtering.[64–67] To apply bioactive glasses as coatings, there are four common methods: enamelling or glazing, flame spray coating, rapid-immersion coating and sol–gel coating.[30]

The bioactive coating materials have the excellent bioactivity of the bioactive glasses or ceramics, as well as the advantageous mechanical properties of metals or alumina. The bone-bonding capacity of these coating may help provide cementless fixation of orthopedic prostheses, especially in short term stabilization of the implants. But in long term implantation, the bioactive coating materials have deficiencies with respect to reliability of the coating/implant interface.

1. The bioactive glass coated implants have great variation in interfacial strength because of bubbles at the glass–metal interface. The studies show that it is difficult to obtain high reliability in a glass–metal coating because of the low SiO_2 content of the bioactive glass. If microporosity is present at the interface low failure strengths occur.[30]
2. Nonresorbable, highly crystalline HA coatings have been used for cementless bioactive fixation to provide an enhanced quality of bone apposition and rate of fixation for long term prostheses.[68] However, *in vivo* experiments show the instability and particulate debris reactions at the bone/coating/implant interface will reduce efficacy in the longer term. The failure may be associated with coating thickness, as well as other chemical and physical properties.[69,70]
3. It is known that the initial cellular response is partly dependent on the proteins absorbed on to the surface. As proteins from the biological fluids come in contact with synthetic surfaces, it is hypothesized that conformational changes of the protein structure result, thereby affecting cellular adhesion.[20,21,71] Recently, it has been reported that the *in vivo* cellular response could be compromised by highly crystallized HA ceramics, indicating that some amorphous or more soluble phases in the coating would be more desirable.[72] *In vivo* studies showed that completely resorbable calcium phosphate coatings trigger steps for enhanced bone apposition rather than fibrous tissue encapsulation on rough surfaces and eliminate interfacial problems even in the presence of a 2–3 mm implantation gap.[73] A resorbable Ca/P coated implant may prove to be an alternative to the nonresorbable HA coating when a gap is present in a non-load-bearing application.

7 MOLECULAR TAILORING OF SURFACE CHEMISTRY

Many surface chemical features of an implant are required for formation of a stable interfacial bond with tissues. In bone, the central issue seems to be

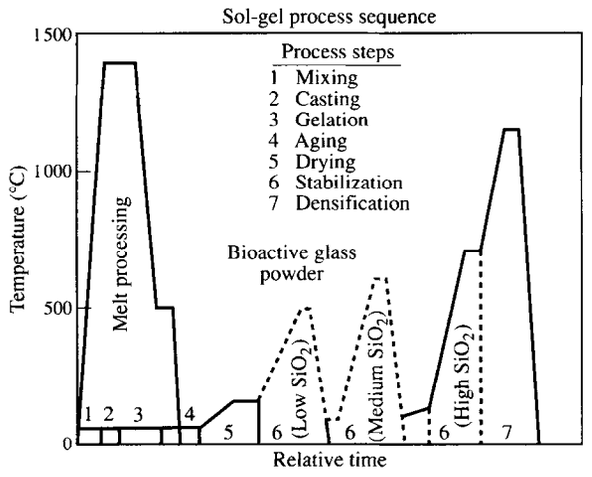

Fig. 5. Processing steps in making bioactive gel-glasses by the sol–gel method.[74]

the relative competition between fibrogenesis and osteogenesis at the interface. Cell culture experiments suggest that highly chemically specific attachment mechanisms control the cell morphology, influence the structure of cell membranes, and activate intracellular functions or transport required for progenitor cell differentiation.[26–28] For example, one of the features of bioactive ceramics is to favour proliferation of osteoblasts over fibroblasts and develop a bone-bonding interface with bone.[1] For this reason, current research is directed towards molecular tailoring of surface chemistry.

7.1 Bioactive gel-glasses

Sol–gel processing is a chemically based method for producing ceramics, glasses, glass-ceramics and composites at much lower temperatures than the traditional processing methods. The sol–gel method has been used to make a new generation of bioactive glasses.[74–76] Seven steps are involved in making gel-glasses or ceramics by the sol–gel method, as shown in Fig. 5.[29]

A lower temperature compared with melt processing of a low SiO_2 bioactive glass is noted. Alkoxide-based sol–gel derived SiO_2–CaO–P_2O_5 glasses have an expanded compositional range of bioactivity over glasses or ceramics made by traditional processes. The bioactive gel-glass compositions in mole percent are given in Table 8.[29] Gel-derived glasses with as much as 88% SiO_2 develop a hydroxyl carbonate apatite layer in SBF, whereas the limit for melt-glasses is 60%. Melt-glasses with > 55% SiO_2 require several days to form a polycrystalline HCA layer, whereas gel-glasses do so within minutes of exposure to physiological solutions.[77] This is because the sol–gel process has the ability to control the material's surface chemistry which directly relates to the bioactivity. The main surface chemistry differences between gel-glasses and melt-glasses are:

1. Gel-glass has a larger volume fraction of nanometre porosity on the surface.
2. Gel-glass has a larger concentration of silanols on the surface.
3. Gel-glass has metastable three-membered and four-membered siloxane rings on the surface. Thus, the bioactivity of gel-glasses can be controlled by regulating the surface chemistry, such as the rate of soluble silicon release and the surface texture. It is predicted that bioactive gel-glasses have a potential use as a drug release system for bone growth factors, for bioactive composites and as coatings of polymers.

7.2 Surface modification

In order to obtain a bioactive material with a Young's modulus which is close to that of bone, Tretinnikov *et al.* developed a bioactive polymer by using surface modification to immobilize organic compounds. An organophosphate polymer was chemically bound on to a polymer film by surface graft polymerization of a phosphate-containing monomer.[78] As the phosphate group is one of the building blocks of HA and has a high affinity toward calcium ions, polymeric materials modified by surface-grafted water-soluble organophosphate polymer induce the deposition of Ca and PO_4 ions in the form of an HCA layer. It is expected that

Table 8. Composition (mole%) of bioactive gel-glasses[74]

Designation	SiO_2	CaO	P_2O_5
49S	50	46	4
54S	55	41	4
58S	60	36	4
63S	65	31	4
68S	70	26	4
72S	75	21	4
77S	80	16	4
86S	90	6	4

Table 9. Clinical applications of bioactive materials

Material	Clinical application	Reference
Bioglass®	Middle ear device, Tooth root replacement, Periodontal treatment, Maxillo-facial reconstruction, Bone defect filler	9,84,94,95
Ceravital®	Middle ear device	13,94,97
Bioverit®	Middle ear device, Tooth root, Spacer	14,85
A/W BG	Vertebrae prosthesis, Vertebral spacer, Iliac crest prosthesis, Bone defect filler	86,87,88
HA	Middle ear device, Tooth root, Periodontal treatment, Maxillo-facial reconstruction, Percutaneous device, Bone defect repair	35,60,89,90,91,94
PE/HA	Orbital floor	92,93,95

covalent immobilization of organophosphates will open the way for developing bioactive bone-bonding polymers. Other surface modification techniques are also used to improve the properties of biomaterials. Takaoka *et al.* found the magnitude of the fatigue of A/W glass-ceramic can be further decreased by Zr ion implantation.[79] A glow-discharge treatment was used by Sendax and Baier to improve the bonding potential of calcium-phosphate-coated implants.[80] Thus, many different methods of surface modification are being explored. Few, as yet, have reached clinical trials.

7.3 Molecular orbital modelling calculation

Quantum mechanical molecular orbital (MO) calculation is a new direction of research to understand the surface reaction of implants and tissues, such as reaction stage 6 in Fig. 3.[8] Using MO calculations, it has been shown that metastable clusters, formed from a condensation reaction of neighbouring surface silanols, can act as heterogeneous nucleation sites for HCA crystals.[81] The metastable silica clusters can also act as preferential adsorption sites for amino acids such as alanine.[82] The MO calculations also show that adsorption of protein molecules on the inorganic surface depends on the binding sites on the protein molecules. This may lead to an understanding of the selective adsorption and subsequent desorption of proteins that act as growth factors or enzymes. Thus, there is hope that the MO method can predict the various biological interactions that occur with Class A bioactive material and provide a means for predicting which material can be used to repair diseased or aged bone.

8 CLINICAL APPLICATIONS OF BIOACTIVE MATERIALS

Biomaterial science involves both biology and material science and engineering. It has developed into an important division of the biomedical field. At present, the total value of the biomaterials in clinical applications is more than $2.7 billion every year in the USA.[83] Twenty five years development of bioactive materials make them increasingly important as clinical materials. As a result of biomechanical limitations, Bioglasses®, glass-ceramics and HA are mainly used in low or non-load bearing situations or compressive load situations in solid or powder form, such as bone restoration and augmentation, middle ear repair, vertebral and iliac crest replacements. All these applications take the advantage of bioactivity and minimize mechanical property requirements.

Table 9 summarizes some of the present clinical applications of bioactive materials. Ten year clinical results are now available for middle ear prostheses and endosseous ridge maintenance implants made from bioactive glass (45S5 Bioglass®). Their clinical performance is an improvement over previously used bioinert implants or Class B, osteoconductive implants, as shown in

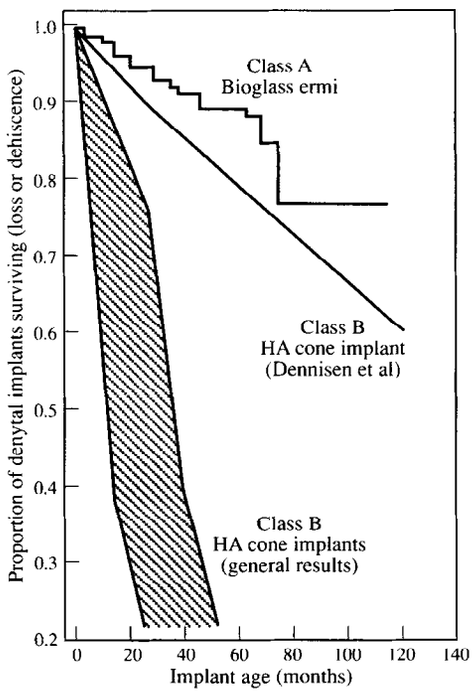

Fig. 6. Survivability of alveolar ridge maintenance implants.[95]

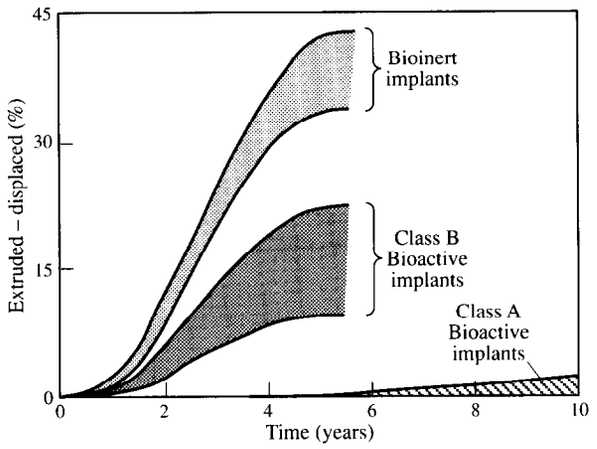

Fig. 7. Extrusion–displacement rate vs time of implantation for various middle ear ossicular replacement.[94]

Figs 6 and 7. A/W glass-ceramic has a higher strength than other bioactive ceramics. It has been used in spine and hip surgery of patients with extensive lesions or bone defects, and the results were quite satisfactory in more than 200 cases.

Although numerous bioactive composites and coatings have been investigated (Tables 5–7), the long term *in vivo* performance of many of these materials is still uncertain. Thus, extensive testing is necessary before they are used in load bearing clinical applications. At present, only several bioactive composites and bioactive coatings have been used clinically. PE/HA composite with a volume fraction of 0.4 of HA has been used clinically as an implant for reconstruction of the orbital floor.[93] The particular properties of the composite allows the implant to be shaped by the clinician during the operation and to be implanted without any fixation.[92] The widest clinical use of HA coatings is on metallic dental endosseous and subperiosteal implants, and on metallic orthopedic devices such as total hips and knees.[96] A percutaneous electrode coated with Bioglass® has been used in clinical application to provide a soft tissue seal for an electronic implant which passes through the skin.[2,84]

9 SUMMARY

Most existing biomaterials were developed based upon trial and error optimization. Further studies on material surface chemistry, material grain-boundary attack or slow crack growth under standardized conditions, protein absorption, molecular biology, and genetic engineering are needed to obtain long-term (> 20 years) reliable biomaterials. There is a hope that in the future biomaterials can be designed having optimized both biochemical and biomechanical compatibility molecularly tailored for specific clinical applications. There is also the opportunity to use the concept of bioactive control of interfacial chemistry to regenerate tissues rather than replace them, as is currently done in the clinic.

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