

# Bioceramics : Processing Routes and Mechanical Evaluation

## 生体セラミックス : 作製方法と機械的特性評価

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**An improved understanding of currently used bioceramics in human implants and in bone replacement materials could contribute significantly to the design of new generation prostheses and post-operative patient management strategies. Overall, the benefits of advanced ceramic materials in biomedical applications have been universally appreciated, specifically, in terms of their strength, biocompatibility and wear resistance. However, the amount of supporting data is not large and the continuous development of new characterization tools is pertinent for better understanding of the microstructure-properties relationship and in general for obtaining new directives for their further improvement. This paper gives an overview and re-examines key-issues which concern both processing and applications of ceramics as biomaterials. With doing this, we attempt to bring to the attention of the ceramic community the issues in current bioceramics.**

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### 1. Introduction

From early as a century ago artificial materials and devices have been developed to a point where they can replace various components of the human body. These new artificial materials have the ability to function within the harshest of environments, and within the living tissue they can operate without any adverse reaction or rejection by the body. These are known as 'Biomaterials.' Biomaterials by definition are "a non-drug substance suitable for inclusion in systems which augment or replace the function of bodily tissues or organs." These materials should be capable of being in contact with bodily fluids and tissues for prolonged periods of time, whilst eliciting little if any adverse reactions.<sup>1)</sup>

Some of the earliest biomaterial applications were as far back as ancient Phoenicia where loose teeth were bound together with gold wire and ligatures were used for tying artificial ones to neighbouring teeth. In the early 1900's bone plates were successfully implemented to stabilise bone fractures and to accelerate their healing. While by the time of the 1950 to 60's, blood vessel replacement experiments were in clinical trials and artificial heart valves and hip joints were in development.

Even in the preliminary stages of this field, surgeons and engineers identified materials and design problems that resulted in premature loss of implant function through mechanical failure, corrosion or inadequate biocompatibility of the component. These observations determined that the key factors in a biomaterial usage are its biocompatibility, biofunctionality, and availability to a lesser extent. Ceramics may be ideal candidates with respect to all the above functions, except for their brittle behaviour. In particular, the absence of an intrinsic toughening mechanism, which on the microscopic scale allows local stress release by plastic deformation, represents the most remarkable difference between biogenic hydroxyapatite and synthetically prepared hydroxyapatite. In this paper, we shall revisit the presently available bioceramics, their preparation methods, their mechanical properties, and their applications, in comparison with biogenic and other biomaterials.

### 2. Overview of bioceramics and other biomaterials definitions and classification of biomaterials

When a man-made material is placed within the human body, tissue reacts towards the implant in a variety of ways depending on the material type. The mechanism of tissue interaction (if any) depends on the tissue response to the implant surface. In general there are three terms in which a biomaterial may be described in or classified into representing the tissues responses. These are bioinert, bioresorbable, and bioactive.<sup>2)-4)</sup> The term bioinert refers to any material that once placed in the human body has minimal interaction with its surrounding tissue, examples of these are stainless steel, titanium, alumina, partially stabilised zirconia, and ultra high molecular weight polyethylene. Generally a fibrous capsule might form around bioinert implants hence its biofunctionality relies on tissue integration through the implant.

Bioactive refers to a material, which upon being placed within the human body interacts with the surrounding bone and in some cases, even soft tissue. This occurs through a time-dependent kinetic modification of the surface, triggered by their implantation within the living bone. An ion-exchange reaction between the bioactive implant and surrounding body fluids results in the formation of a biologically active hydrocarbonate apatite (calcium phosphate) layer on the implant that is chemically and crystallographically equivalent to the mineral phase in bone. Prime examples of these materials are synthetic hydroxyapatite [ $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ ],<sup>5),6)</sup> glass-ceramic A-W<sup>7)</sup> and bio-glass<sup>8)</sup>.

Bioresorbable refers to a material that upon placement within the human body starts to dissolve (resorbed) and slowly replaced by advancing tissue (such as bone). Common examples of bioresorbable materials are tricalcium phosphate [ $\text{Ca}_3(\text{PO}_4)_2$ ] and polylactic-polyglycolic acid copolymers. Calcium oxide, calcium carbonate and gypsum are other common materials that have been utilised during the last two decades. There are four basic classes of materials used in clinical practice for biomedical implants and devices. Those being, bioceramics, metallic alloys, polymers and their composites. These classes of materials have combinations of properties determined by the composition and the production methods utilised, while each set of

properties has its own benefits and limitations.

#### Bioceramics

Bioceramics used singularly or with additional natural, organic or polymeric materials are amongst the most promising of all biomaterials. Interest in ceramics for biomedical applications has increased over the last twentyfive years. Ceramics are considered hard, brittle materials with relatively poor tensile properties with excellent compressive strength, high resistance to wear with favourably low frictional properties. The low frictional properties is enhanced by the fact that ceramics are hydrophilic with good wettability and can be highly polished which provides a superior load bearing surface with itself or polymeric material in physiologic environment.

The ceramics that are used in implantation and clinical purposes include aluminum oxide (alumina), partially stabilised zirconia (PSZ) (both yttria [Y-TZP] and magnesia stabilised [Mg-PSZ]), bioglasses, glass-ceramics, calcium phosphates (hydroxyapatite and  $\beta$ -tricalcium phosphate) and crystalline or glassy forms of carbon and its compounds.

Alumina is used for orthopaedic and dental implants it has the ability to be polished to a high surface finish accompanied by its bioinert property in physiological conditions and high hardness it has been implemented in wear bearing environments.<sup>11,9)</sup> An example of which has been stated above where it has been implemented in total hip arthroplasties (THA) as the femoral head generating reductions in wear particles from ultra-high molecular weight polyethylene (UHMWPE). Other applications for alumina encompass porous coatings for femoral stems, porous alumina spacers (where bone excavation has been necessary) and in dentistry for tooth implants.<sup>10)-12)</sup>

Compared to alumina, Mg-PSZ has higher flexural bend strength, fracture toughness and Weibull modulus, as well as lower Young's modulus and the ability to be polished to a superior surface finish.<sup>13)</sup> The higher fracture toughness is of importance in femoral heads due to the tensile stresses induced by the taper fit onto the femoral stem. Although not quite as hard as alumina, Mg-PSZ still possesses excellent wear resistance and has been proposed and used for similar orthopaedic applications as alumina.<sup>12)</sup> Wear rates of UHMWPE against magnesia partially stabilised zirconia have been found to be low enough such that tribological debris would not be a problem in clinical applications.<sup>14),15)</sup> Preliminary results indicate that the use of a ceramic-ceramic femoral head/acetabular cup system is advantageous over ceramic/UHMWPE systems as polymeric wear debris is avoided.<sup>16)</sup> In fact Chevalier et al.<sup>17)</sup> found that the coefficient of friction between an alumina cup and zirconia head was much lower than ceramic against UHMWPE, and the resultant wear between the two components was almost zero. Recent work by Clarke et al.<sup>15)</sup> on articulation of femoral heads in total hip replacement (THR) using hip simulators with alpha-calf serum as a lubricant, which alumina/alumina, zirconia/alumina, and zirconia/zirconia couples were investigated has shown that wear rates using zirconia/zirconia exhibit a mild run-in phase as opposed to a more evident run-in phase when comparing to alumina/alumina articulation, followed by little observable weight change thereafter. Typically alumina/alumina wear revealed steady weight loss trend after a run-in phase. While zirconia/alumina wear, where zirconia was the head and the liner alumina, showed little weight loss and the alumina liner revealed a typical run-in phase followed by steady weight loss. The study has revealed promise for hard/hard THR systems whereby wear rates were three times less in order of magnitude when compared to PE cups. The study has employed an alpha-calf serum at a 50% concentration

whereby most other studies published were carried out using either water or saline solution which can be quite detrimental to the performance of the ceramic in question.

The glasses that have been investigated for implantation are primarily based on silica ( $\text{SiO}_2$ ), which may contain small amounts of other crystalline phases. The most prominent and successful application of this is Bioglass<sup>®</sup>, which can be found in detail in various comprehensive reviews.<sup>4),18)-20)</sup> Bioactive glass compositions lie in the system  $\text{CaO-P}_2\text{O}_5\text{-SiO}_2$ . The first development of such a bioglass began in 1971 when Hench first proposed his 45S5 bioglass with a composition of 45%  $\text{SiO}_2$ , 24.5%  $\text{CaO}$ , 24.5%  $\text{Na}_2\text{O}$ , and 6%  $\text{P}_2\text{O}_5$  by weight.<sup>8)</sup> Hench,<sup>4)</sup> and Vroouwenvelder et al.,<sup>21)</sup> suggested that bioglass 45S5 has greater osteoblastic activity as compared to hydroxyapatite. The reasoning behind this was due to a rapid exchange of alkali ions at the surface, which in turn over a period of time leads to the formation of a silica rich layer. This then allows for the migration of  $\text{Ca}^{2+}$  and  $\text{PO}_4^{3-}$  ions to the silica rich surface where they combine with soluble calcium and phosphate ions from the solution, where the formation of an amorphous  $\text{CaO-P}_2\text{O}_5$  layer takes place. This layer undergoes crystallisation upon the interaction of  $\text{OH}^-$ ,  $\text{CO}_2^{3-}$  and  $\text{F}^-$  from solution. Similar phenomenon have been observed by other researchers of bioglass with similar compositions.<sup>22),23)</sup>

Li et al.,<sup>24)</sup> prepared glass ceramics from a similar composition with differing degrees of crystallinity and found that the amount of glassy phase remaining directly influences the formation of an apatitic layer, with total inhibition when the glassy phase constituted less than about 5 mass%. Due to the surface-active response of these types of materials, they have been accepted as bioactive (or surface-active) biomaterials and have found applications in middle ear implants and other non-load bearing conditions.

Calcium phosphate ceramics were proposed as early as the 1920 for biomedical applications because tri-calcium phosphate, injected into defects, demonstrated more rapid bone growth and union than the untreated defects. Hydroxyapatite (HAp) was first identified as being the mineral component of bone by DeJong.<sup>25)</sup> However, it was not until the 1970s that synthetic hydroxyapatite [ $\text{Ca}_{10}(\text{PO}_4)_2(\text{OH})_2$ ] was accepted as a potential biomaterial that forms a strong chemical bond with bone *in vivo*, while remaining stable under the harsh conditions encountered in the human body.

Hydroxyapatite and  $\beta$ -tricalcium phosphate [ $\beta\text{-Ca}_3(\text{PO}_4)_2$ ] are the primary calcium phosphates that have been implemented as biomaterials.  $\beta$ -tricalcium phosphates have been used successfully, as fillers for bone defects to stimulate the formation of new bone.<sup>26)</sup> However, this study showed that after a 12 month period,  $\beta$ -tri-calcium phosphate was observed to have been totally absorbed. It is thought that these calcium phosphates could be used as implants or as bone replacement/defect fillers. It was aimed that these materials will be used to fill voids in bone structure that will dissolve over a period of time while the resorption takes place, and the bone re-growth or advancement takes place at similar rates. These properties place hydroxyapatite and other calcium phosphates into the class of inorganic biomaterials known as bioactive materials.<sup>27)</sup> The only other inorganic materials that fall into this highly specialized classification are the biocompatible glasses and glass ceramics (Table 1).

The dissolution rates of some of these materials under simulated physiological conditions have been investigated with emphasis placed on hydroxyapatite,  $\beta$ -tricalcium phosphate and tetra-calcium phosphate. Under *in vitro* conditions, the solubility of these materials has been shown to

Table 1. Solubility Products of Various Calcium Phosphate Compounds

Chemical Name	Abbr.	Chemical Formula	Phase	Ca/P	Space Group	Solubility Product
Monocalcium Phosphate Hydrate	MCP	Ca(H <sub>2</sub> PO <sub>4</sub> ) <sub>2</sub> H <sub>2</sub> O	-	0.50	-	1.0x10 <sup>-3</sup>
Dicalcium Phosphate Hydrate	DCPD	CaHPO <sub>4</sub> ·2H <sub>2</sub> O	Brushite	1.00	2/m	1.87x10 <sup>-7</sup>
Dicalcium Phosphate Anhydrous	DCPA	CaHPO <sub>4</sub>	Monetite	1.00	P1	1.26x10 <sup>-7</sup>
Octacalcium Phosphate Pentahydrate	OCP	Ca <sub>8</sub> H <sub>2</sub> (PO <sub>4</sub> ) <sub>5</sub> ·5H <sub>2</sub> O	-	1.33	-	5.01x10 <sup>-15</sup>
β-Tricalcium Phosphate	TCP	Ca <sub>3</sub> (PO <sub>4</sub> ) <sub>2</sub>	β-Whitlockite	1.50	R3c	2.83x10 <sup>-36</sup>
Penta-calcium Hydroxyl Phosphate	HAp	Ca <sub>5</sub> (PO <sub>4</sub> ) <sub>3</sub> OH	Hydroxy-Apatite	1.67	P6 <sub>3</sub> /m	2.35x10 <sup>-59</sup>
Tetra-calcium Phosphate Monoxide	TCPM	Ca <sub>4</sub> O(PO <sub>4</sub> ) <sub>2</sub>	Hilgenstockite	2.00	P2 <sub>1</sub>	-

decrease in the order of:<sup>28),29)</sup>

Tetra-calcium phosphate > β-Tricalcium Phosphate > Hydroxyapatite

It has been stated that hydroxyapatite is "scarcely resorbable"<sup>30),31)</sup> and therefore, hydroxyapatite's potential to be implemented for osseous implant purposes is justified.

#### Metallic alloys

Metallic alloys have proved themselves as excellent biomaterials due to their properties in fracture fixation (Table 2). There are three main metallic alloys that have been established as suitable for orthopaedic implants. Those being low carbon steel alloys (316L stainless steel), cast cobalt based alloys (cobalt chrome and molybdenum), and titanium (commercially pure or titanium alloy-aluminium 6%, vanadium 4% (Ti6Al4V)). Of which their biocompatibility has been well understood and documented.<sup>11),32)</sup>

Of the three, titanium when mixed in the ratio of Ti-13Nb-13Zr, has been reported to be particularly outstanding in their ability to form a hard, abrasion-resistant ceramic surface layer with an oxidative treatment and have

improved biocompatibility.<sup>33)-35)</sup> New generation zirconia surface converted zirconium metal for ceramic knee applications is one of the most recent additions into this highly competitive field.

Fracture fixation of an implant includes screws, plates, nails, and their various mutations and combinations. These implants require biocompatibility and the requirements of strength, ductility and elasticity. Because of these requirements and the usually applied fixation methods, if too rigid there is an increased probability of bone resorption and possible bone fracture when the implant is removed during a revision surgery.

Titanium alloys (Ti6Al4V and Ti-13Nb-13Zr) have the benefit of good strength to weight ratio and are relatively inert in the human body, and the sensitivity are rare. Ducheyne et al.<sup>36)</sup> found that even though vanadium and aluminium are released over time within the body, there was no appearance of any adverse reaction. Their modulus of elasticity and specific gravity are half that of stainless steel and cobalt chromium alloys<sup>37)</sup> (cf. Table 2). The effect of stress shielding with the use of titanium alloys is rare and therefore, the implant does not generally have to be removed from the patient and lower specific gravity imparts lighter and less obtrusiveness to the recipient.<sup>38)</sup> However, tissue discoloration observed during revision surgery has generated a common resistance from the orthopaedic fraternity.

#### Polymers

Most types of polymers used for biomedical purposes are homopolymers: polymethylmethacrylate (PMMA), 2-hydroxyethyl methacrylate (HEMA or PHEMA), polyethylene (PE), polypropylene (PP), nylon, polydimethyl siloxane (PDMS), polytetrafluoroethylene (PTFE). Others are copolymers: polyglycolide lactide (PGL), hexafluoropropylene (FEP), and polyurethanes (PU). Due to the chemical compositions and molecular structure, UHMWPE and high-density polyethylene (HDPE), and recent cross-linked polyethylene (HCPE) are the most stable polymers available for implant use (bioinert).

A good example of the use of HDPE is the total hip replacement carried out in 1962 by Charnley, where the HDPE was used for the acetabular cup.<sup>39)</sup> This particular design has continued and in early 70's a metal alloy stem was employed with an alumina femoral head on a UHMWPE acetabular cup. This design during the last 25

Table 2. Mechanical Properties of Biomaterials

	YOUNGS MODULUS GPa	COMPRESSIVE STRENGTH MPa	TENSILE STRENGTH MPa	POISSONS RATIO	DENSITY g/cm <sup>3</sup>	FRACTURE TOUGHNESS MPam <sup>1/2</sup>	HARDNESS Knoop
<b>METALS</b>							
Titanium Alloy (Ti-6Al-4V)	114	450-1850	900-1172	0.34	4.43	44 - 66	3200
Cr-Co-Mo	210	480-600	400-1030	0.29	8.3	120-160	3000
Stainless Steel (316L)	193		515-620	0.30	8.0	20 - 95	
<b>CERAMICS</b>							
Alumina	420	4400	282-551	0.27	3.98	3- 5.4	2300
Zirconia (TZP)	210	1990	800-1500	0.31	5.74-6.08	6.4-10.9	1400
Silicon Nitride (HPSN)	304	3700	700-1000	0.30	3.3	3.7 - 5.5	1600
Hydroxyapatite (3% porosity)	7-13	350-450	38-48		3.05-3.15		
<b>HUMAN TISSUE</b>							
Cortical Bone	3.8-11.7	88-164	82-114	0.28	1.7-2.0	2-12	130-170
Cancellous Bone	0.2-0.5	23	10-20	0.32			
Cartilage	0.002-0.01		5-25				
<b>OTHER</b>							
Bone Cement (PMMA)	2.24-3.25	80	48-72		1.19	0.7-1.6	
UHMWHD Polyethylene	0.69	20	38-48	0.20	0.94		

years has reportedly reduced wear rates by as much as 10 to 20 times<sup>40,41</sup> as compared to wear rates metal-on-metal alone. It has been widely reported that, wear particles produced during articulation can cause severe tissue reaction, abrasion, and eventual loosening of the implant, which is accompanied by severe discomfort to the patient and revision surgery is required. However, some recent reports based on some of the metal/metal implants', 30 years survival success, somehow rekindled a new interest in the use of highly polished metal/metal hip implant use in both Europe and USA markets.

#### Composites

During the last 5 years bone cement materials has grown in popularity and are a very promising osteoconductive substitutes for bone graft. They are prepared like acrylic cements and contains range of powders such as monocalcium phosphate, tri calcium phosphate and calcium carbonate, which is mixed in a solution of sodium phosphate. These cements are produced without polymerisation and the reaction is nearly non-exothermic. The final compounds are reported to be 10–100 MPa in compression while 1–10 MPa in tension although very weak under shear forces. It is currently used in orthopaedics in the management of fractures. It has been suggested that this material could improve the compressive strength of the vertebral bodies in osteoporosis. Injection of calcium phosphate cement is feasible and it may improve their compressive strength.<sup>42)</sup>

Preparation of hydroxyapatite/ceramic composites through the addition of various ceramic reinforcements has been attempted, metal fibres,<sup>43)</sup> Si<sub>3</sub>N<sub>4</sub> or Al<sub>2</sub>O<sub>3</sub> whiskers,<sup>44)</sup> Al<sub>2</sub>O<sub>3</sub> platelets<sup>45,46)</sup> and ZrO<sub>2</sub> particles.<sup>47,48)</sup> In many cases, the composites could not be successfully prepared and, because of problems related to a poor densification, the mechanical properties could not be improved.

Hydroxyapatite/metal and hydroxyapatite/polymer composites are two typical classes of materials, which have been examined for improving the toughness characteristics of synthetic hydroxyapatite.<sup>49)–53)</sup> In both cases, a toughness improvement can be found, due to a crack-face bridging mechanism operated upon plastic stretching of metallic or polymeric ligaments. This mechanism is the same as that which improves the toughness characteristics of natural bones above those of synthetic (dense) hydroxyapatite.<sup>53)</sup> Zhang et al.<sup>54)</sup> proposed a toughened composite consisting of calcium hydroxyapatite dispersed with silver particles. This material was obtained by a conventional sintering method. It was reported that the toughness of these composites increased up to 2.45 MPa·m<sup>1/2</sup> upon loading the mixture with 30 vol% Ag. The use of silver is not only for taking advantage of the ductility of silver in terms of fracture toughness, but also because silver is inert and has antibacterial properties.<sup>55)</sup> de With and Corbijn<sup>50)</sup> used metal (Hastelloy X and Fe-Cr-alloy) fibres as reinforcement for hydroxyapatite. Some of their composites could be fully densified by hot-pressing at temperatures below the decomposition temperature of hydroxyapatite to tricalcium phosphate and tetracalcium phosphate. Fracture toughness was improved by a factor 6 as compared with monolithic hydroxyapatite material, with a maximum value of 7.4 MPa·m<sup>1/2</sup> for the FeCr-alloy-containing composite. The bending strength of this composite was also higher (i.e., >200 MPa) than that of monolithic hydroxyapatite. However, despite the improvements in strength and toughness, the benefit of a composite structure on other mechanical properties, above other monolithic ceramics or metals does not seem to be universally accepted.

### 3. Processing of hydroxyapatites for biomedical applications

#### Bone grafts

Bone grafting is currently used in orthopaedic and maxillofacial surgery for the treatment of bridging diaphyseal defects, non-union, filling metaphyseal defects and mandibular reconstruction. Autogenous bone graft is osteogenic (which have an inherent capacity to form bone, due to living cells such as osteocytes or osteoblasts), osteoconductive (have no capacity to form bone or induce its formation but they provide an inert scaffold which osseous tissue can utilise to regenerate living bone), osteoinductive (stimulate cells in the wound to undergo phenotypic conversion to osteoprogenitor cell types capable of formation of bone). There are no substitutes for autogenous bone; there are, however, synthetic alternatives. Allografts have been used as an alternative, but it has low or no osteogenicity, increased immunogenicity and resorbs more rapidly than autogenous bone; most importantly, transmission of disease remains a concern.

In clinical practice, fresh allografts are rarely used because of immune response and the risk of transmission of disease. The frozen and freeze-dried types are osteoconductive but are considered, at best, to be only weekly osteoinductive. Freeze drying diminishes the structural strength of the allograft and renders it unsuitable for use in situations in which structural support is required. Allograft bone is a useful material in patients who require bone grafting of a non-union but have inadequate autograft bone. Bulk allografts can be utilised for the treatment of segmental bone defects.<sup>56)</sup> Their use is well documented for reconstruction after resection of bone tumours, however not common in reconstruction after trauma in which bone lengthening and transport are usually required.

#### Composites for graft applications

Demineralsed bone matrix (DBM) can induce heterotopic bone, the active components of DBM being a series of glycoproteins, which belong to a group of transforming growth factor superfamily (TGF- $\beta$ ). The members of this superfamily are responsible for the morphogenetic events involved in the development of tissue and organs. A protein can be isolated from the bone matrix, which is termed as the bone morphogenic protein (BMP). DBM is commercially available and used in management of non-union of fractures. They are not suitable where structural support is required. To date, the main delay in developing clinical products has been the need to find a suitable carrier to deliver the BMP to the site at which its action is required. New generation ceramic composites/hybrids could fill this gap. Experimentally, BMP-2 and OP-1 (BMP-7) have been shown to stimulate the formation of new bone in diaphyseal defects in the rat, rabbit, dog, sheep and non-human primates.<sup>57)</sup> The use of BMP's with new calcium phosphate derivatives or composites could be used for bone remodelling where bone regeneration and remodelling is needed such as therapeutic applications in osteoporosis.

Bovine collagen may be mixed with hydroxyapatite and is marketed as a bone-graft substitute, which can be combined with bone marrow aspirated from the site of the fracture. Although no transmission of disease has been recorded, their use will continue to be a source of concern. This material is osteogenic, osteoinductive and osteoconductive, however it lacks the structural strength required.

Calcium Sulphate (Plaster of Paris) or its composites are one of the oldest osteoconductive materials available. They have been used to fill bony defects however its main drawback is the chemical reaction that occurs during setting which results in non-homogeneous crystalline structure with variable properties. It also resorbs very rapidly at a rate,

which exceed the capacity of surrounding bone to regenerate.

#### Hydroxyapatite coatings from simulated body fluids

One of the most promising methods in bioceramics has been the introduction of simulated body fluids (SBF) by Kokubo and co-workers.<sup>58),59)</sup> A hydroxyapatite layer can be easily produced on various organic or inorganic substrates in an acellular simulated body fluid with ion concentrations nearly equal to those of the human blood plasma.<sup>58)</sup> Further analysis of the surfaces showed that it contained very fine crystallites of carbonate ion containing apatite (Fig. 1). Osteoblasts have been shown to proliferate and differentiate on this apatite layer.<sup>60)</sup> Subsequent chemical bond can generate a faster healing and longevity.

Body fluid is a metastable solution and if an apatite nucleating functional group is present on a substrate within the body fluid, the apatite spontaneously nucleates. It has been reported that this nucleation rate increases if excessive  $\text{Ca}^{2+}$  ions,  $\text{PO}_4\text{H}_2$ , and  $\text{Si-OH}$ ,  $\text{Ti-OH}$ ,  $\text{Zr-OH}$ ,  $\text{Ta-OH}$ ,  $\text{Nb-OH}$  or similar functional groups are present.<sup>59)</sup>

#### Hydroxyapatite coatings by sol-gel and other methods

Due to the reason that porous hydroxyapatite has unfavourable mechanical properties it is not used as a monolithic structure for implantation under load bearing purposes. This has seen the investigation of hydroxyapatite being used as a thin film coating on metallic alloys. Because hydroxyapatite is bioactive, using it as a thin film on biometallic alloys enables the coupling of the two materials primary properties to form a functional single component.<sup>61)</sup>

Of the metallic alloys investigated titanium based alloys have shown to be the material of preference for thin film coating.<sup>62)</sup> Titanium alloys possess good mechanical strength and fatigue resistance under load bearing conditions. They tend to be lightweight, with high strength to weight ratios and it is not uncommon for these alloys to be three to four times stronger than aluminium.

Of the coating techniques investigated, thermal spraying tends to be the most commonly used and analysed. This technique has been faced with challenges of producing a controllable resorption response in clinical situations. Be-

sides the set backs, thermally sprayed coatings are continually being improved. However, other techniques are being investigated. A driving factor behind these other techniques can be attributed to the finding on sputtered hydroxyapatite coatings that only a submicrometric coating thickness is sufficient to simulate carbonate apatite deposition under in vivo conditions.<sup>63)</sup>

Techniques that are capable of producing thin coatings include pulsed-laser deposition<sup>64)</sup> and sputtering<sup>65)</sup> which, like thermal spraying involves high-temperature processing. Other techniques such as electrodeposition<sup>66),67)</sup> and sol-gel<sup>68)</sup> utilise lower temperatures and avoid the challenge associated with the structural instability of hydroxyapatite at elevated temperatures.<sup>69)</sup>

The sol-gel technique is categorised as an intermediate temperature method, which, like other methods has the ability to produce either an amorphous or crystalline coating. However, the key factors are that it results in a stoichiometrically homogeneous coating due to mixing on the molecular scale; reduced firing temperatures due to small particles sizes with high surface areas; ability to produce uniform fine-grained structures; use of different chemical routes (alkoxide or aqueous based); and their ease of application to complex shapes with a range of coating techniques those being dip, spin, and spray coating.<sup>70)</sup> The lower processing temperature is an added advantage, it avoids the phase transition ( $\sim 883^\circ\text{C}$ ) in the titanium (based alloys) used for biomedical devices.

#### Coralline apatites by hydrothermal method

These materials are derived from the sea coral. The pore structure of coralline calcium phosphate produced by certain species is similar to human cancellous bone, making it a suitable material for bone graft (Fig. 2).

Coral is composed of calcium carbonate in the form of aragonite. As coral is a naturally occurring structure it has optimal strength and structural characteristics. Coral has been used as bone grafts and orbital implants since the 1970s as the porous nature of the structure allows in-growth of blood vessels to create a blood supply for bone, which will eventually infiltrate the implant. Pore interconnection sizes are of utmost importance when hard and soft tissue in-growth is involved. Kühne et al.<sup>71)</sup> showed that implants with average pore sizes of around  $260\ \mu\text{m}$  had the most successful in-growth as compared to no implants (simply leaving the hole empty). It was reported that the interaction of

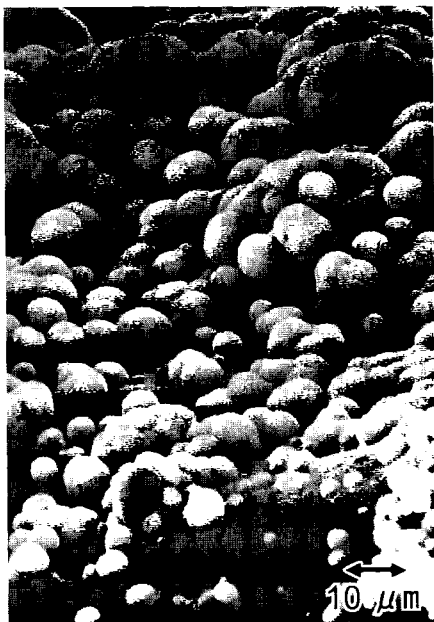


Fig. 1. SEM micrograph of apatite formation on silica and titania gels in SBF solution (after Kokubo et al.<sup>59)</sup>).

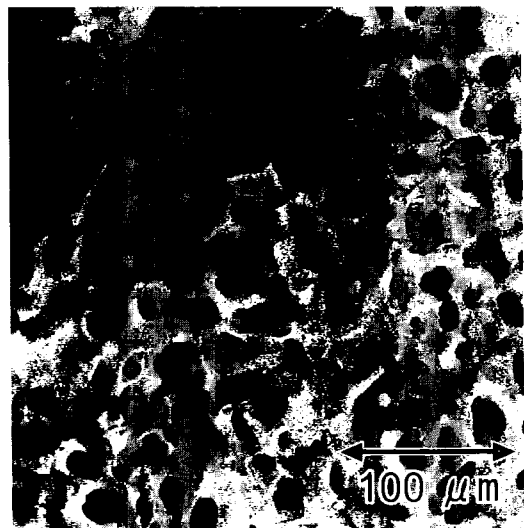


Fig. 2. Coralline structure after conversion to hydroxyapatite.

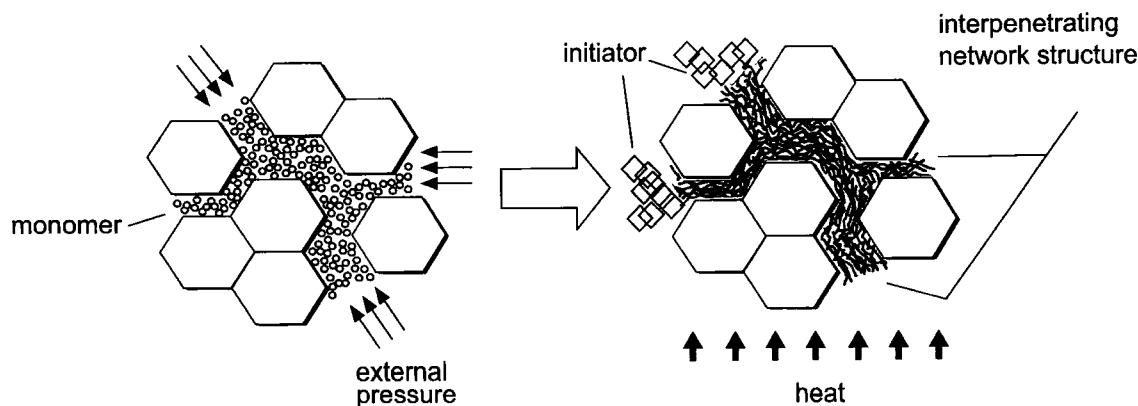
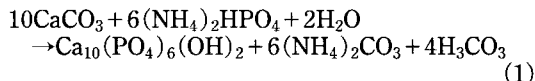


Fig. 3. Schematic diagram of the *in situ* polymerisation synthesis route.

the primary osteons between the pores via the interconnections that allows propagation of osteoblasts.

The hydrothermal method was first used in 1974, for hydroxyapatite formation directly from corals by Roy et al.<sup>72)</sup> It was reported that complete replacement of aragonite ( $\text{CaCO}_3$ ) by phosphatic material was achieved under  $270^\circ\text{C}$  and 103 MPa using the hydrothermal process. In 1996, HAP derived from Indian coral using hydrothermal process was reported by Sivakumar et al.<sup>73)</sup> However, the resultant material was in the form of a powder and required further forming and shaping. Hydroxyapatite is said to replace the aragonite whilst preserving the porous structure. During the hydrothermal treatment the following exchange takes place:



The resulting material is known as coralline hydroxyapatite, whether in the porous coralline structure or in powdered form.

Hu et al.<sup>74)</sup> succeeded to convert Australian coral to 100% hydroxyapatite by using the hydrothermal method and a patented process based on alkoxide sol gel coating. They have reported 120% increase in the biaxial strength of the treated coral in comparison to unconverted one.

Novel processing routes to biomimetic hybrid composites

The conventional way to synthesize an inorganic material-based composite is to subject a mixture of the constituent phases to heat treatment. This process is also common in the biomaterials production field, however, it is conceptually far from the biomineralization process from body fluids which occurs in nature. The natural process makes it available fine hybrid structures, which are hardly reproducible by sintering. In recent years, several research groups have demonstrated the feasibility of *in vitro* techniques for the synthesis of biomimetic material structures.<sup>58),75)-78)</sup> However, the superior sophistication of the biological route has not been paired yet and these techniques, so far, with an exception of Kokubo's very inventive SBF method, have not proved to be fully applicable for actual use.

Obviously, a traditional sintering route is not directly applicable to produce ceramic/polymer composites because no polymer will stand at the densification temperature of any ceramic material.

Dense hybrid materials were obtained, opening a completely new perspective in biomaterials for artificial bone substitutes.<sup>79)</sup> A new alternative route, based on an *in situ* polymerization process, carried out into an inorganic

scaffold with submicrometer-sized open porosity, has been recently proposed.<sup>52),53)</sup> This method is an intermediate one between conventional sintering and biomineralization *ex vitro*, because it still employs sintering for the preparation of the inorganic scaffold, but the subsequent hybridisation of the scaffold with organic phases is carried out through a chemical route, thus avoiding high-temperature heating procedures. This method enables the synthesis of biomimetic (hybrid) inorganic/organic composites and while aiming at a relatively complex structural designs, it is based on a simple and easily reproducible process. A schematic of this efficient synthesis route is given in Fig. 3.

#### 4. Fracture behavior and toughening mechanisms in biogenic materials and synthetic composites

A common characteristic of natural biomaterials such as bone,<sup>80)</sup> nacre,<sup>81)</sup> sea urchin tooth<sup>82)</sup> and other tough hybrid materials in nature is the strong microscopic interaction between the inorganic and the organic phases. This characteristic allows the organic phase to act as a plastic energy-dissipating network, forming stretching (bridging) ligaments across the faces of a propagating crack. In biological materials, the crack-face bridging mechanism is governed by structures hierarchically designed at a nanoscale level. Such complexity has led to the common perception that, in considering which methods can be used to mimic natural design, *in situ* synthesis techniques should be adopted. Precipitation *in situ* of calcium carbonate or hydroxyapatite into a polymeric matrix, for example, has been proposed as a novel synthetic route to biomimetic composites.<sup>75),83)</sup> Despite significant advances in understanding biological mineralization and developing new fabrication processes, the composites to date obtained by these methods are by far *in embryo* for actual applications, due to their low structural performance.

Figure 4 shows the results of fracture tests carried out on two natural biomaterials, bovine femur and Japanese nacre (*Crassostrea Nippona*), in comparison with a synthetic hydroxyapatite/nylon-6 composite (obtained by *in situ* polymerisation of  $\epsilon$ -caprolactam infiltrated into a porous apatite scaffold) and a dense monolithic apatite obtained by sintering. The higher work of fracture achieved in inorganic/organic hybrid materials, as compared to that of the dense monolithic hydroxyapatite, is due to stretching of protein or polymeric ligaments across the crack faces during fracture propagation (Fig. 5).

Although the microscopic architecture of human manufactured composites will still remain behind that of natural materials, mimicking natural microstructures while

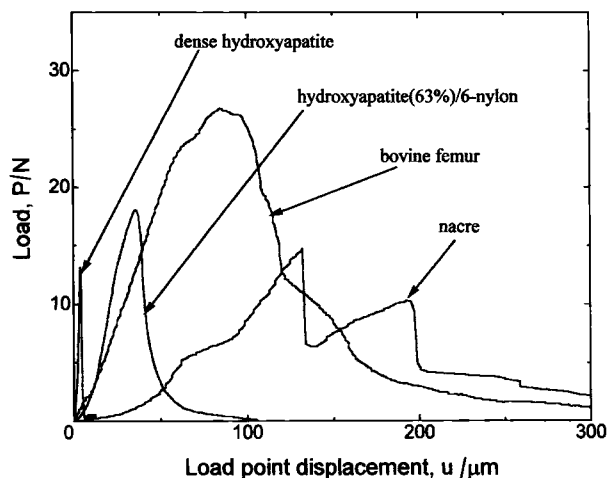


Fig. 4. Results of fracture tests carried out on two natural biomaterials, bovine femur and Japanese nacre (*Crassostrea Nippona*), in comparison with a dense synthetic hydroxyapatite obtained by traditional sintering, and a synthetic hydroxyapatite/nylon-6 composite obtained by *in situ* polymerisation of  $\epsilon$ -caprolactam infiltrated into a porous apatite scaffold.

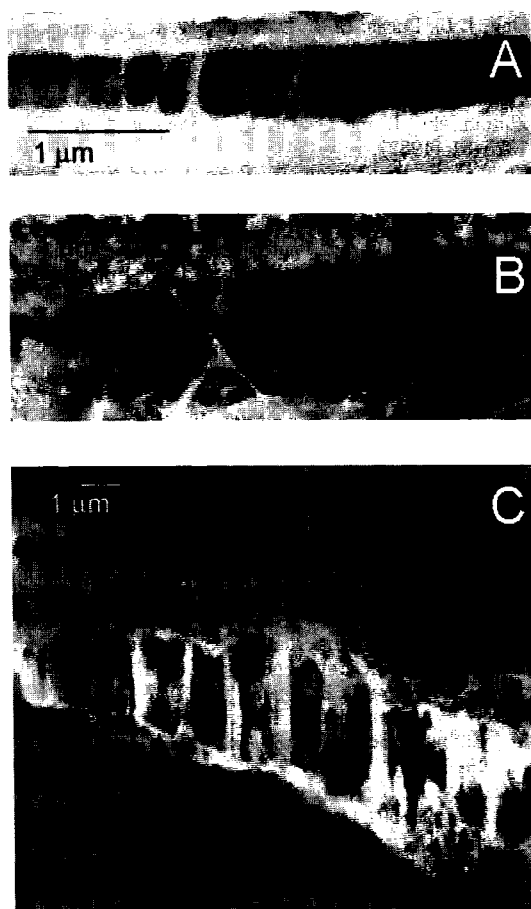


Fig. 5. Protein and polymeric ligaments stretched across the crack faces during fracture propagation in (a) Japanese nacre, (b) bovine femur, and (c) hydroxyapatite/nylon-6 composite.

using strong synthetic molecules may lead to a new generation of synthetic biomimetic materials, whose toughness

characteristics are comparable with the toughest materials available in nature. A formidable challenge remains the optimisation of bioactivity characteristics in these novel hybrid composites.

## 5. Conclusions

In this paper, we have revisited some of the key-issues related to both processing and applications of bioceramics as compared with other available biomaterials. We believe that with an improved physical insight into microscopic phenomena and understanding of stress related mechanisms, major fundamental issues in the biomedical field, which stand still unsolved, can be further investigated and new insights achieved. However, this will require a more intense collaboration among medical doctors, ceramists, physicists and technologists to achieve substantial team-work in the bioceramics field. We hope to contribute with this overview to promote in the near future collaborations both nationally and internationally (e.g., between Japan and Australia) to trigger substantial improvements in this complex and important field.

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