

Bioceramics — A New Era

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In the last few decades with the introduction of bioceramics, a special class of ceramics to perform tailored functional / biological / chemical activities in living systems, treatment procedure through reconstructive surgery has been revolutionized and this has resulted in marked improvement in quality of life of the rehabilitated persons. The procedure involves an innovative use of specially designed ceramics for reconstruction of diseased / damaged parts of body, e.g. hips, knees, wrists, spines, jaws, diseased long-bones and repair for maxillofacial, periodontal disease, etc. Bioceramics are produced in a variety of compositions, forms and phases and are often used in the form of bulk materials of specific shape to perform a special function, which are called implants, prostheses or prosthetic devices. They are also used in powder / granule forms to fill space of the damaged hard tissues, which through natural repair process get integrated and restore function, and as coatings to provide bio-friendly interface on substrate for cementless fixation and sometimes also as a second phase in composites. In this review, different classes of bioceramics, their chemical compositions, structures, tailored functions and broad application areas have been outlined and the effects of their usage on treatment of different trauma / degenerative diseases have been discussed. Along with the current research status of the advanced laboratories around the world on this emerging subject, the developments made so far at CGCRI, Kolkata have also been outlined.

[Keywords : Bioceramics, Calcium phosphates, Bone substitutes, Prosthetic devices]

Introduction

Since long, ceramics have been used in different health care systems although their usages are restricted within external applications only, particularly for manufacture of eyeglasses, diagnostic instruments, chemical ware, thermometers, chromatographs, tissue culture flasks, etc. In addition, the domain has covered the wide spectrum of dental restorative materials, e.g. gold porcelain crowns, glass filled ionomer cements and many other materials used for bridges and crowns. The use of ceramics *in vivo* as implants is a newly explored area (≤ 30 years), which are generally used to alleviate pain and restore function of the diseased / damaged part of the body. Figure 1 depicts various parts of the human skeletal structure, which require replacement by prosthetics on damage. A major contributor to the need for 'spare parts' for the body is progressive deterioration of tissue with age. With growing age, the natural hard tissues in our systems, which are natural living composites of calcium phosphate based ceramics and collagen are especially vulnerable to fracture because the osteoblasts (bone growing cells) become less productive in elderly persons that lead to reduction of bone density and strength.¹ This effect is observed to be more severe on women because of hormonal changes associated with menopause. In this stage the progressive reduction in density greatly deteriorates the strength of trabecular / cancellous bones of vertebrae, which are even otherwise very porous and fragile (Fig.1). This leads to the fracture of hip, knee joints, collapsed vertebrae / spine which needs to be repaired immediately to restore the normal function of the limb. In recent years, it has been noted that with increasing rate of average life expectancy, the need of replacement of old / damaged bones has significantly increased. Further,

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rapid economic globalization has compelled people to adopt a faster life-style that in turn has increased the number of accidents manifold, leaving trauma victims who require replacement of their damaged limbs. To address the need for intervention in these cases, many materials are currently in use, which include natural autografts (tissue harvested from the same patient) and allografts (tissue harvested from a similar species) as well as a variety of biomaterials based on ceramics, metals, polymers and a host of composites. The use of allografts is limited by the possibility of an immunological response and risk of disease transmission whereas autografts are restricted by a limited number of donor sites and are associated with an additional trauma resulting from the collection of the bone tissue. In this scenario, man-made materials stand out as a potential solution, being easily available as also amenable to processing and modification to suit the needs of a given application, though many problems persist resulting from the inability to match exactly the natural tissue.² Metals suffer from inferior corrosion / wear resistance and higher elastic modulus far exceeding those of bone that in turn leads to stress shielding and subsequent weakening of the host bone tissue, making it susceptible to re-fracture. Polymers used for similar application lack rigidity, hardness and ultimate mechanical properties required in load bearing applications. Many bioceramic compositions have been tested for use in the body,^{3,4} however, only few have been studied up to human clinical application. Clinical success in this regard requires simultaneous development of a stable interface with connective tissues and a match of mechanical behaviour of the implant with the tissue to be replaced. Moreover, high chemical inertness, absence of adverse effects on the surrounding tissue, long-term life expectancy, fatigue strength and absence of effects on the free metabolic

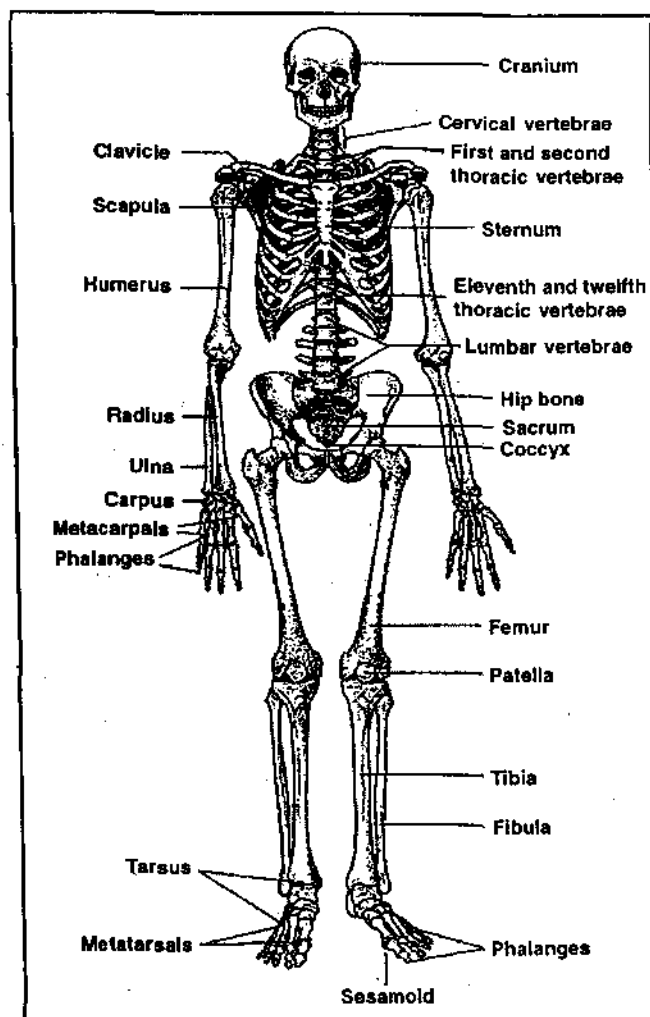
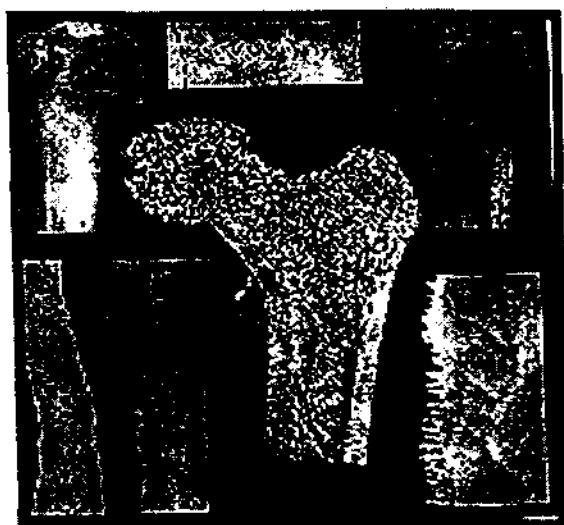
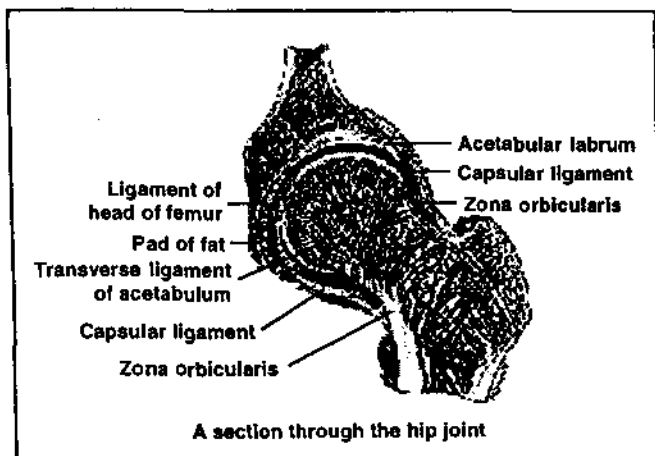


Fig. 1 - Various parts of the human skeletal structure, which require replacement by prosthetics on damage.

process are some other criteria, summarized under the term 'biocompatibility' for these materials that need to be studied in detail prior to insert them to living system. The clinical success of bioceramics has led to a remarkable improvement in the quality of life for millions of people. The bioceramic materials represent one of the most important of the ceramic research, development, production and quality assurance in this century and have opened a worldwide market with an annual turnover of \$12 billion with a current growth rate of 7-12% per annum.

The success of bioceramics in hard tissue replacement primarily depends on the fact that natural bone is a supportive living tissue composed of a carbonate containing calcium apatite (~60 wt%) in type I collagen (~30 wt%) matrix. It also contains ~10 wt% water. The mineral component of bone is a form of calcium phosphate / calcium apatite known as hydroxyapatite (HAp). Stoichiometric HAp has a molecular formula $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, whereas the bone mineral contains many substitutions like magnesium, sodium, potassium, fluoride, chloride and carbonate ions. This apatitic mineral is closely associated with collagen fibres (highly aligned, anisotropic structure) to yield flat, plate like nanocrystals ($40 \times 10 \text{ nm}^2$). The organic matrix

renders the tensile strength whereas the mineral component gives rise to compressive strength of bone. Two types of bone can be distinguished: cortical bone which has ~90% solid bone tissue and trabecular bone which is spongy and contains 80% marrow filled with voids. Bone is a dynamic tissue subject to constant deposition by osteoblast activity and subsequent resorption by osteoclasts. When a new surface is introduced into the bone tissue, a sequence of complex interactions is triggered.⁵

Implanted *in vivo*, all prosthetic materials elicit a response from the host tissue which varies with the bulk / surface properties of that particular material. The bioceramic materials are classified according to this property which is summarized in Table 1.

In addition, in some cases, when a bioinert / bioactive bioceramic is porous, bone in-growth occurs which mechanically attaches the bone to the material. This type of attachment may be termed 'biological fixation' at the site of the damaged tissue.

Bioinert Ceramics

Although usage of ceramics for bone and tooth repair began in medieval ages, its introduction and postopera-

Table I : Classification of bioceramics

Sl. No.	Type of bioceramics	Mechanism of attachment	Type of attachment	Example
A	Bioinert	Bone growth occurs into the surface irregularities by cementing / press fitting into a defect	Morphological fixation	Al ₂ O ₃ / ZrO ₂
B	Bioactive	Attached directly by chemical bonding at the surface	Bioactive fixation	Bioactive glasses/ glass-ceramics/ dense HAp
C	Resorbable	Slowly replaced by bone	—	Calcium sulphate, tricalcium phosphate, some bio-active glasses

tive follow-up have been scientifically reported at first as the femoral head of a hip prosthesis in the last decade of nineteenth century. In 1890, the first experimental prosthesis used by Gluck in Germany consisted of a carved ivory ball and socket fixed in place with bone glue composed of resin, pumice powder and plaster of Paris. However, these early experimentations on human patients and many others were not successful as during those days the knowledge of stress analysis at the hip under different dynamic postures was not perfect and in addition the material available was with inadequate strength and limited reliability. During the period 1890-1950, there were a number of changes in the design and development of hip implants. In 1938, Wiles in London used total hip prosthesis made of stainless steel consisting of a femoral and an acetabular component. In 1948 and 1950, McBride and Eicher introduced smooth intramedullar stem and a femoral neck collar. In 1951, Haboush in New York used self curing acrylic cement for fixation of vitallium total hip prosthesis. In 1950, Thompson developed vitallium prosthesis, which had a flared collar below the head and a vertical cemented intramedullary stem. This design, though modified, is still in use. In 1952, Austin Moore, with Bohlmann, developed a 'self-locking' prosthesis, which featured a fenestrated stem to allow bone in-growth. This design has stood the test of time and is still used for selected femoral neck fractures. In 1962, introduction of stainless steel femoral stem and a high-density polyethylene cup, both cemented into place by methacrylate cement improved long-term results dramatically. In 1968, Chamley prosthesis was released for general use, which is still very much in existence without any major changes in the design. Cobalt-chromium alloy (27-30% Cr, 5-7% Mo, balance: Co) was first introduced by Freeman as an alternative to stainless steel in implant manufacture. The material has better wear properties than stainless steel. This is designed to be used without cement and hence, there are holes in the structure for bone in-growth. The top section of the prosthesis is roughened

to increase friction and stability while the bottom surface is polished to prevent the stem from rubbing against the bone tissues inside the bone canal, which may generate wear debris. Further, it was noticed that titanium and its alloys have very high strength, excellent corrosion resistance and low stiffness in comparison to stainless steel or cobalt-chromium alloys. Therefore, it reduces the effect of stress shielding. It has been universally accepted as the best suitable metal for any prosthetic application. Recently, the trend is to combine the best mechanical properties of all the materials described above and to adopt appropriate engineering design in order to develop an implant with the optimum chance of long-term clinical survival. The process started with a cobalt-chromium based Freeman implant with nitride surface finish, fitted with ceramic femoral head. The stems were coated with hydroxyapatite to harden the surface of the stem, prevent scratching and in turn reduce release of the metal wear debris.

However, along with the changes in life-style, the ideal design of hip-prosthesis has never been obtained and even today the search is on for the most suitable one. A few of the newer variety with the ceramic components are presented in Fig. 2. The major long-term problem with cemented hip replacement is the loosening of the bond between implant and the bone that often needs a second surgery to fix it once again. This has led to the development of the cement-less hip replacement in which the surface of the metal part is porous. The most remarkable evolution has been in the area of porous coating along the stem and number of porous layers. Initially it was a full-length coating and with two to three layers, while the current trend is to give single layer coating towards proximal-end. Only a few years ago bone in-growth fixation was most desirable, while currently more importance is given to tissue stabilization at the interface. Judging from the multiple interrelated factors of fixation and durability, it is believed that the ideal prosthesis would have a tight fitting that stabilizes itself and achieves equilibrium. Since fibrous interposition is an inevitable biological consequence under dynamic load against implant material, the crucial issue is how one can make the fibrous tissue remain stable, thin and inactive. Absence of macro-motion of the implant is expected to play a vital role. Thus, if the design of the implant follows the anatomic shape and size of recipient bone, the interference fit is possible to result in a pain-free joint, which would serve for a long time.

At present, every year about 0.6 million hip replacement operations takes place globally while in India alone the number is around 50,000. This figure in India may rise to an average of 0.4 million once common people become economically strong enough to bear the huge medical expenses, associated with such operations. Women, of 55-60 years of age group, who usually after menopause suffer from osteoporosis, specifically need these prostheses to serve for more than 25 years of their life span. The conventional hip joints made out of stainless steel / Co-Cr alloy / Ti-6Al-4V alloy last only for about 10-15 years and therefore need to be replaced several times which involves risk and enormous expenditure. For the purpose, mainly with

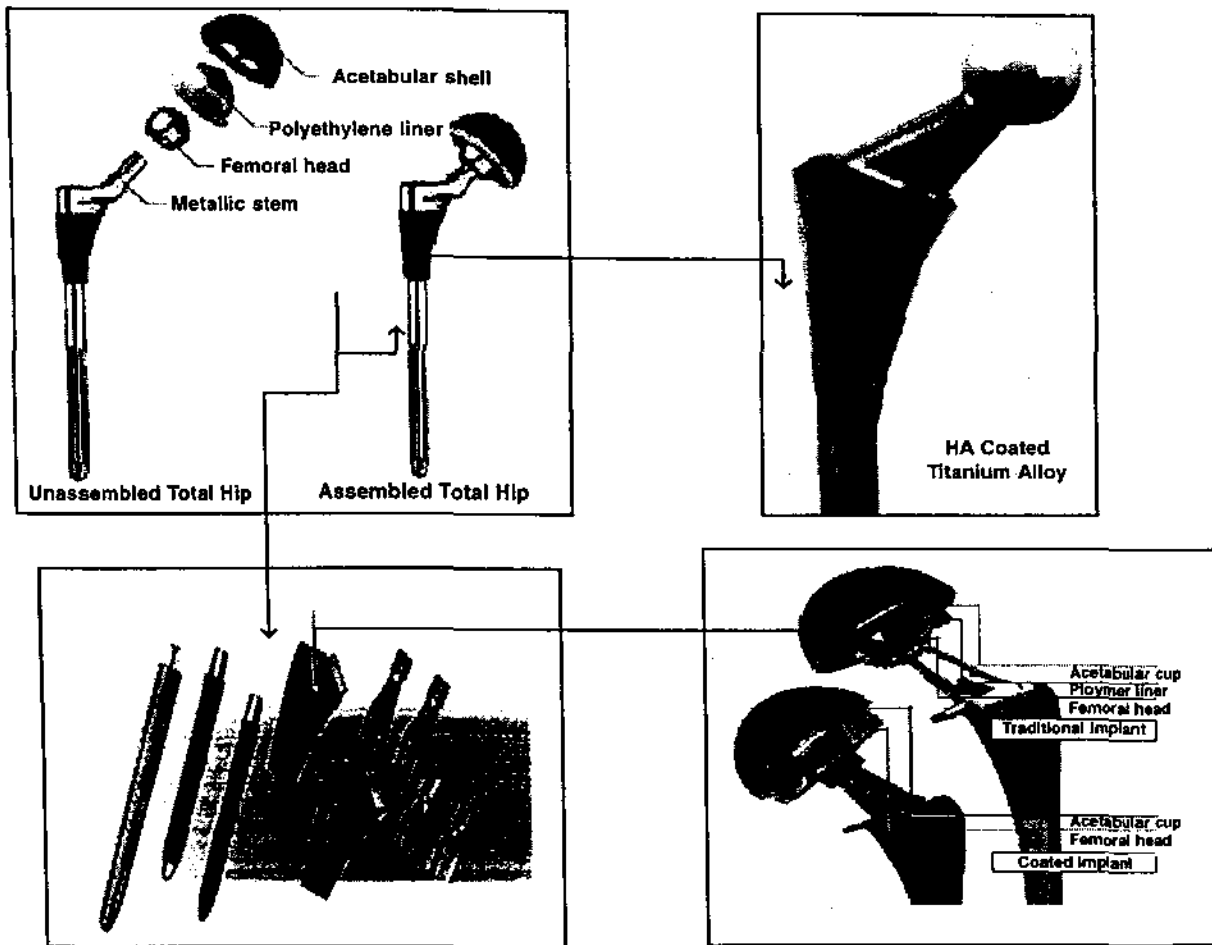


Fig. 2 – Evolution of hip implant designs.

an expectation to provide longer trouble-free life, bioinert ceramics are replacing metals, particularly for femoral head applications, and at present globally about 10% of the femoral components of total hip joints are made out of ceramics. Tetragonal zirconia polycrystals (TZP), zirconia toughened alumina (ZTA), zirconia and fine-grained alumina are the most widely used bioinert (that exhibit minimum interaction with the surrounding tissues) ceramic materials that can render trouble-free service for more than 20 years. Although properties like inherent hardness, chemical inertness, low deformation and creep are favourable, very low fracture toughness / strength has restricted further use of the material in musculo-skeletal prosthetics. As a result of an extensive research, bioinert ceramics with average grain size of 200 nm have been obtained that offer very high strength (>1000 MPa) and fracture toughness (>5 MPa^{1/2}). These nano-structured ceramics with much improved properties are expected to be used by the practicing surgeons in large scale and with much higher degree of confidence. Though the previous applications of the bioinert ceramics were confined to the articulating surfaces of artificial joints and load bearing skeletal components, recently, efforts are also being made to develop ceramic-based acetabular cup of a hip joint. This is expected to extend the life span of a hip joint for more than 20 years

and the item has already been introduced in the human system in 2002. Also, to meet the requirements of knee joint prostheses, bioinert ceramic femoral components have been used in Australia recently that may provide a longer service life over the conventional metallic ones (10-12 years) (Fig.3).

Alumina (Al₂O₃)

Al₂O₃ (α-Alumina) has been used in orthopaedic surgery for more than 20 years in total hip prosthesis and dental implants. The other clinical applications of this biomaterial include knee prosthesis, bone screws, alveolar ridge and maxillofacial reconstruction, ossicular bone substitution, keratoprosthesis and segmental bone replacement etc. All these are due to combination of a range of structural properties — corrosion resistance, biocompatibility, wear resistance, low friction and high strength.^{3, 6-11} Medical grade alumina offers two main advantages over other materials (e.g. metals / polymers), : (i) low wear rates and (ii) low concentration of wear particles (debris) in the surrounding tissue. The corrosion resistance of alumina ceramics is also very high (rate of corrosion 10⁻⁴ g.cm⁻² / day corresponding to a maximum corrosion rate of 1 mm in 10 years) and therefore the material is termed as 'biologically inert'.

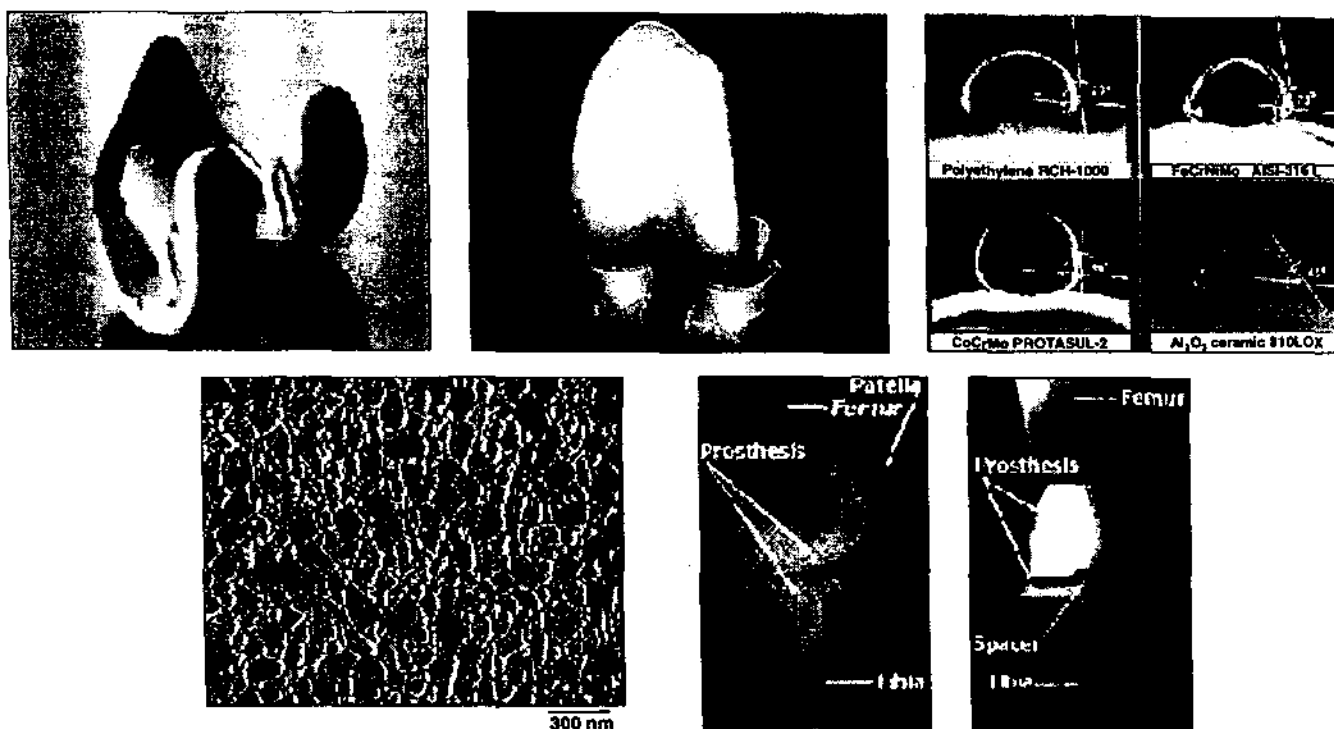


Fig. 3 – Total knee-joint prosthesis showing (clockwise from left) : femoral components, SEM of surgical grade alumina, XRD of the prosthesis, side view and rear view.

The biocompatibility of surgical grade alumina has been ensured by means of animal tests and clinical experience over a long period of time. Superior tribological properties of high-density, small grain size ($< 4 \mu\text{m}$, having a very narrow size distribution) resulted in an exceptionally low coefficient of friction and minimal wear rate^{6, 7, 12} and this has established the credentials of the material as the articulating surface in total hip / knee prostheses. Extensive characterization of the material to predict suitability for long time usage under typical biological condition points out that Al_2O_3 that meets or exceeds ISO (International Standards Organization) specifications has excellent resistance to dynamic / impact fatigue and also to sub-critical crack growth.^{12, 13} Detailed gate analysis of human hip has pointed out¹⁴ that during walking, the maximum load encountered by a hip of a 100 kg body weight person is about 4.3 KN (Fig. 4a). To assess the trouble-free service life of these prostheses, the ceramic based hip joint balls were exposed to 10^8 walking cycles (which is equivalent to 20 years of walking) of the persons with varied body weight up to 400 kg and it was observed that the balls could withstand the test parameters. The average breaking load of the balls before and after the fatigue study was determined following the ISO specified parameters to observe that up to 300 kg body weight persons there was no degradation of properties which indicate that even after such a stringent stress exposure there was no appreciable sub-critical crack growth within these balls. However, exposure to the equivalent stress experienced from a person with 400 kg body weight degraded the properties of the balls to some extent and the results of this study are reflected in Fig. 4b. The study concluded that the balls with uniform and sub-micron

average grain size would improve the fatigue properties of these balls even further and eventually fatigue life of the prostheses would be longer. An increase in average grain size to $>7 \mu\text{m}$ can decrease the mechanical properties by a considerable amount. Therefore, a small amount of MgO ($<0.5\%$) is used as a sintering aid to limit the grain growth during the sintering process.

The strength requirements of alumina are met by the production process that yields a pore free structure maintaining a very low rate of grain growth. Hot isostatic pressing (HIP) post compaction are sometimes adapted for further reduction of pore size and volume as in ceramics each pore acts as a notch, reducing inert strength and long-term fatigue strength. Alumina with a density of >3.95 (typically 3.97) $\text{g}\cdot\text{cm}^{-3}$ is generally diamond-ground and polished to obtain a surface finish of the following specifications : R_a (average surface roughness) of $0.02 \mu\text{m}$; R_t (maximum value of surface roughness) of $0.5 \mu\text{m}$. Recently, in total hip prosthesis, alumina non-cemented cups are press fitted into the acetabulum (socket) of the hip. The cups are stabilized by bone growth into grooves or around pegs. The mating femoral ball surface also is alumina, which is press fitted into the metallic stem (Fig. 5a). Long-term results of this new generation of hip joint are excellent, particularly for the younger and active patients, although stress shielding can occur.⁷ This is due to the high Young's modulus of alumina¹⁵ which prevents the bone from being loaded. Alumina has 10-50 times higher Young's modulus than the cortical bone (7-25 GPa). This may lead to stress shielding that in turn results in cancellous bone atrophy and loosening of the acetabular cup in older patients with osteoporosis and rheumatoid arthritis⁷ and therefore longer

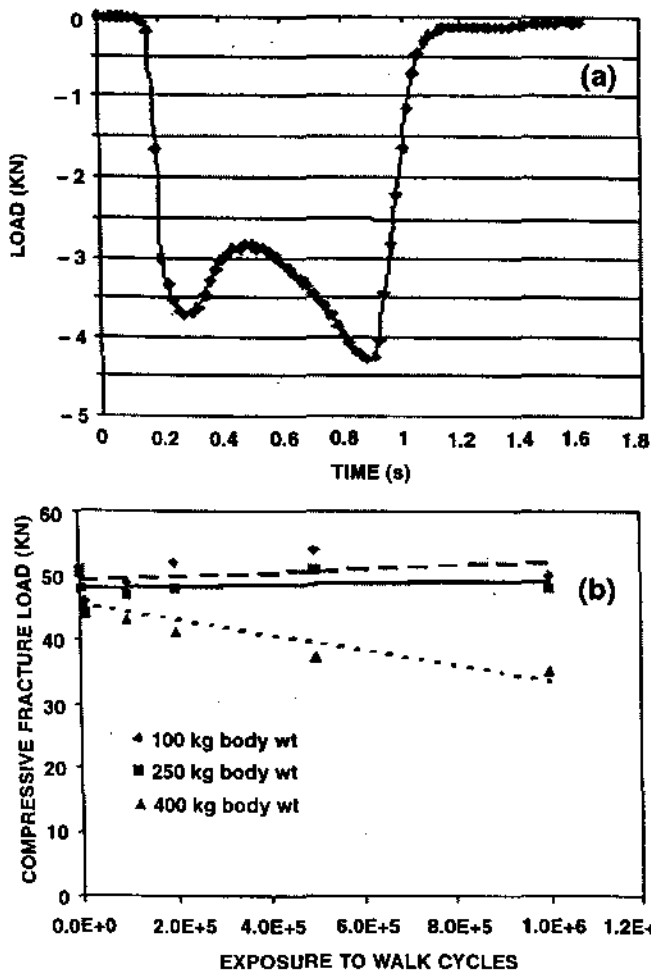


Fig. 4 – (a) Typical stress pattern experienced by a human hip during walking (body weight of the person has been assumed to be 100 kg and (b) fracture strength of the ceramic heads after being exposed to walking cycles of varied conditions.

follow-up of the patients is needed before claiming its phenomenal success.

In India, attempts were made by Central Glass and Ceramic Research Institute, Kolkata, to develop hemi / total hip joint prostheses, in which the femoral heads made of high purity alumina were fitted with modified 'Austin Moore' stainless steel stem for *in vivo* implantation. Table II summarizes the properties of the material and Fig. 5b shows the total and the hemi hip joint prosthesis developed at CGCRI. This has been clinically tried in more than 40 patients in different reputed hospitals in Kolkata and Delhi and the results are very encouraging.^{5, 16} Also, hip joint implants fitted with Thomson, Charnley and Talwalker type stainless steel stems and alumina based ceramic heads fitted into Ti-6Al-4V alloys have been developed subsequently and tried in human patients, successfully.

Zirconia (ZrO_2)

The interest in zirconia derives from its high fracture toughness and tensile strength. These properties make it possible to manufacture femoral heads for total hip prostheses that are smaller than present generation Al_2O_3

Table II : Typical properties of a high-purity alumina for surgical implants (CGCRI) and their comparison with ISO specified values

Properties	Material / item developed at CGCRI	Medical grade alumina as specified by ISO 6474
Density	3.97 g.cm ⁻³	3.90 g.cm ⁻³
Al_2O_3	99.9%	99.5%
$SiO_2 + Na_2O$	0.05%	0.1%
Microstructure (grain size)	~ 1 μm	< 7 μm
Microhardness	2300 HV	2300 HV
Compressive strength	4500 MPa	4000 MPa
Flexural strength	> 420 MPa	400 MPa
Young's modulus	400 GPa	380 GPa
Corrosion resistance	0.008 mg.m ⁻² per day	0.1 mg.m ⁻² per day

heads. The stable form of pure zirconia at room temperature is monoclinic. In tetragonal form, it is stabilized by al-

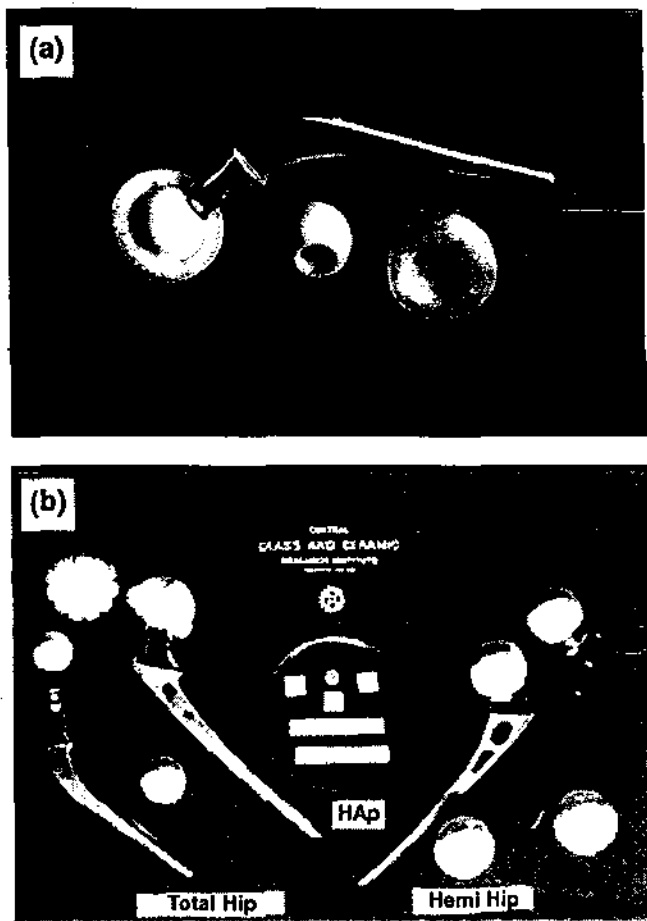


Fig. 5 – (a) Medical grade Al_2O_3 used in total hip replacement – (left): Al_2O_3 acetabular cups mated with Al_2O_3 femoral balls, (centre): Al_2O_3 balls also can be used with ultra-high-molecular weight polyethylene (UHMWPE) cups, (right): alternative metallic stem designs for morphological / cement fixation and (b) Surgical alumina-based total and hemi hip joint prosthesis with UHMWPE acetabular cup and modified "Austin Moore" SS stem, developed by CGCRI

kaline earth (calcium, magnesium) and rare earth (yttrium) oxides. Tetragonal zirconia polycrystals (TZP), an advanced zirconia, is characterized by extremely small grain size (0.5 μm) after sintering. Also, it has higher bending strength, fracture toughness and lower Young's modulus. However, TZP has a lower hardness (1250 HV vs 2300 HV for alumina) and the presence of small traces of thorium / hafnium (present in source minerals) renders certain level of radioactivity in this material. Though biocompatibility of the material is not well documented, it may serve as an additional load bearing material for orthopaedic implant. Also, it may reduce diameter of the femoral head, which improves 3D-mobility of the implant.

Biocarbons

Some of the crystalline forms of carbon are highly biocompatible, chemically inert and thrombo-resistant that make them a preferred material where interface to blood flow is required or as a prerequisite for various biomedical devices. In the form of a bioinert coating, three different classes of carbon are used in biomedical devices: pyrolytic carbon (LTI, low temperature isotropic), vapour deposited carbon (ULTI, ultra low temperature isotropic) and glassy (vitreous) carbon.¹⁷⁻¹⁹ Except LTI, all other carbon materials in clinical use are pure elemental carbon. The extremely well wear resistance and inherent toughness are due to their two-dimensional turbostratic crystal structures (density $\sim 1400\text{-}2100 \text{ kg.m}^{-3}$).

The LTI pyrolytic carbon is produced by chemical vapour deposition at temperatures above 1000°C whereas ULTI carbon is produced by vacuum deposition from gaseous precursors containing carbon. Glassy carbon is made by controlled heating of carbonaceous precursors (e.g. cellulose / phenol-formaldehyde resin) and subsequent elimination of volatile constituents.²⁰⁻²²

Bokros was the pioneer in the medical use (1967) of pyrolytic carbon coatings on metal substrates,²³ its processing and application in heart surgery.²⁴ The first LTI carbon coatings used in human body as a prosthetic heart valve was in 1969 (De Bakey).²⁴ Other than prosthetic heart valve,²² LTI carbons are also used in percutaneous access devices for dialysis,²⁵ for dental implants.¹⁷ Glassy carbons also have application in the same area. ULTI carbons are used as coatings in pacemakers²⁵ and on sealing rings for heart valves.¹⁷

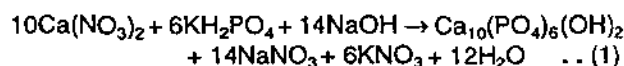
Bioactive and Resorbable Ceramics

Calcium Phosphate Ceramics

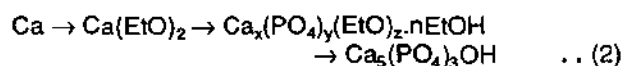
Calcium phosphate ceramics is a well-known inorganic constituent of normal (bones, teeth, fish enamel and some species of shells) and pathological (dental and urinary calculus, stones, atherosclerotic lesions) calcifications. In bone, they occur mainly in the form of poorly crystallized non-stoichiometric sodium, magnesium and carbonate containing HAp (termed as 'biological apatite' or 'dahlite'). There are a number of biologically relevant calcium phosphate ceramics in normal human calcified tissues.⁵ At body temperature, in aqueous media (body fluid), the stable phase is $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ (hydroxyapatite, at $\text{pH} > 4.2$), whereas at

$\text{pH} > 4.2$, the stable phase is $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ (hydroxyapatite, HAp). At higher temperatures, other phases, e.g. $\text{Ca}_3(\text{PO}_4)_2$ (β -tricalcium phosphate, whitlockite), $\text{Ca}_4\text{P}_2\text{O}_9$ (tetracalcium phosphate) are formed. These anhydrous, high temperature calcium phosphate phases interact with water, body fluids at optimum temperature (37°C) to form HAp. The importance of Ca : P ratios in determining the solubility and tendency for resorption in body has been discussed by De Groot,²⁶ Williams²⁷ and Le Geros *et al.*²⁸ It has been observed that presence of micropores in the sintered material increases the solubility of these phases.²⁹⁻³² The induction time to form crystallized carbonated apatite increases as follows: Ca-deficient HAp (cdHA) < poorly crystallized HAp (pcHA) < crystallized HAp (cHA) < coralline HAp (I-HAp) < β -tricalcium phosphate (β -TCP) < calcium carbonate marine coral (I-CC) < β -calcium pyrophosphate (I- β -CP). Among these, the β -TCP and HAp are the two ceramics used widely for clinical application.

Among the different phases of calcium phosphates discussed so far, hydroxyapatite is the main mineral constituent of bone, biocompatible, exhibits no reaction to foreign bodies and is integrated to bone. It is used as an implant material in various forms: as a solid body with little porosity, as granular particles, as porous structure or as coating on metallic implants. Pure HAp can be prepared wet chemically, by solid state reactions or by hydrothermal treatment.³³⁻³⁵ The synthesis technique has a significant effect on the powder morphology, specific surface, stoichiometry and crystallinity. Wet chemical method of synthesis by Klyuchnikov³⁶ is given as:



After gradual crystal growth from the solution, the HAp precipitate is collected on a filter, washed with water and ethanol, and dried at 40° to 50°C . Kibal'chits and Komarov³⁷ described high speed HAp synthesis using potassium compounds instead of sodium and ammonium compounds. Here, HAp is obtained by rapidly mixing $\text{Ca}(\text{NO}_3)_2$ and $\text{Ca}_3(\text{PO}_4)_2$ solutions. The Ca : P atomic ratio, initially 1.58, increases to 1.67 over a period of 6 h. Turova and Yanovskaya³⁸ reported HAp synthesis through the formation of a solution of calcium ethoxide, followed by reaction with phosphoric acid and annealing of the product in air:



In each of these synthesis routes prior to annealing, the reaction product is amorphous as determined by X-ray diffraction. The wet chemical techniques of HAp synthesis involve many process variables, which have adverse effects on the reproducibility of the process and make it difficult to maintain the stoichiometric Ca : P ratio during synthesis and to obtain HAp powder with controlled chemical and physical properties. The main process parameters are the pH of the solution, the reaction temperature and duration.

Dry processes of HAp synthesis involve solid-state diffusion during calcinations of mixtures containing appropriate amounts of Ca^{2+} and PO_4^{3-} ions in the temperature range.

In this case, generally the mixtures of $\text{Ca}_3(\text{PO}_4)_2$ and $\text{CaCO}_3/\text{CaP}_2\text{O}_7$ and $\text{CaCO}_3/\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ and CaO are calcined between 900° and 1300°C in presence of water vapour.³⁹ Dry processes ensure the formation of stoichiometric HAp (Ca : P = 1.67) but require much power (high temperatures) and time. Moreover, the products of such processes typically lack homogeneity.

Hydrothermal synthesis of HAp involves reactions at high temperature and pressure and requires expensive equipment.^{33, 40, 41} According to Yubao *et al.*,⁴² stoichiometric HAp can be prepared under hydrothermal conditions by the following reaction:



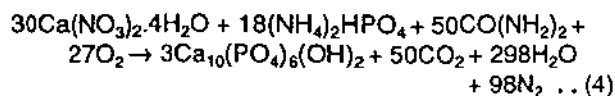
Yubao *et al.*⁴³ have also analyzed the effect of NH_4OH on the growth rate of HAp crystals. In the absence of NH_4OH , the growth of the prismatic crystals took 96 h even at 500°C and 80 MPa. The introduction of NH_4OH was found to substantially raise the reaction rate. Hydrothermal synthesis is commonly carried out in gold capsules. In this, the starting reagents and H_2O must occupy 50-60% of the autoclave volume, depending on the synthesis temperature.

Apart from the above techniques, a number of processes are used less frequently; HAp can be obtained by (a) hydrolyzing a 2:1 mixture of $\text{K}_4\text{P}_2\text{O}_7$ and CaCl_2 for two weeks;⁴⁴ (b) freeze drying a mixture of calcium acetate and triethyl phosphate.³³ These methods offer possibility of preparing fine-particle, high-porosity material.

The solution combustion method for synthesis of nanocrystalline HAp powder is based on the principle of thermochemical concepts used in propellant chemistry. In this, a self-sustaining, self-propagating, non-explosive exothermic, fast combustion reaction between the fuel-oxidizer (metal salt, especially nitrates in aqueous solution) mixture (in stoichiometric ratio) takes place. Urea, tetraformal triaz-

ine,⁴⁵ carbohydrazide,⁴⁶ etc are used as fuels. The choice depends on their 'reducing power' and the amount of gases (CO_2 , H_2O and N_2) generated. In order to release maximum energy, the stoichiometric composition of the precursor redox mixture is calculated on the basis of the total oxidizing and reducing valences of the oxidizer metal salt and of the fuel.

In CGCRI, synthesis of nanocrystalline Ca-hydroxyapatite has been attempted following the solution combustion route:



Heat required for the synthesis as above is provided mainly by the combustion reaction of urea-metal nitrate mixture. This has led to the formation of nanocrystalline Ca-hydroxyapatite powder (size 60-150 nm) and of hydroxyapatite-tricalcium phosphate composites using fuel-rich batches.⁴⁷ The Ca/P atom ratio (range 1.45-1.67) obtained governs the thermal stability of the HAp phase so formed and there is a transformation to tricalcium phosphate phase to yield the composite materials by this process.

HAp has a hexagonal structure (space group $P6_3/m$, two formula units per unit cell) with lattice parameters $a = 0.942$ nm and $c = 0.687$ nm. The ideal formula of HAp is $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$. The Ca atoms reside in two positions: six atoms per unit cell are in position Ca(II) and four atoms in position of Ca(I). Ca(I) is located on the three fold axis and is coordinated by nine oxygens of the phosphate groups (Fig. 6). The Ca(II) atoms form equilateral triangles; within each triangle, a fluorine atom lies on the hexagonal axis, the OH^- group resides in an off-centre position.³³

To produce implants capable of withstanding mechanical loads, it is reasonable to use densely sintered ceramics, which surpass porous ceramics in strength. For load

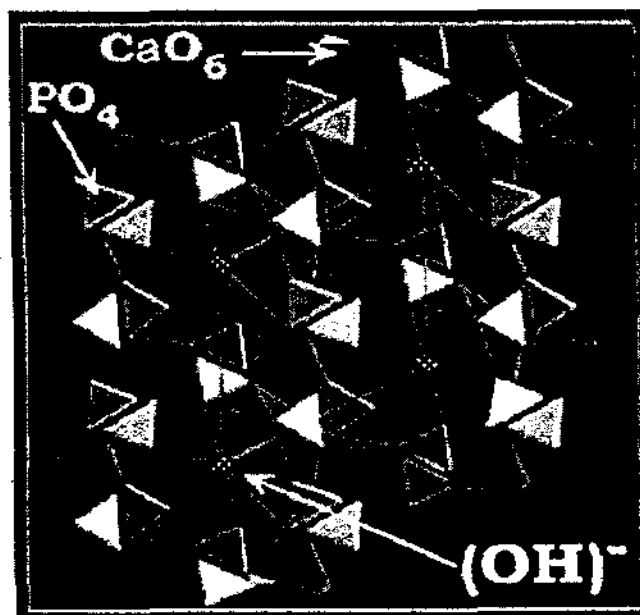
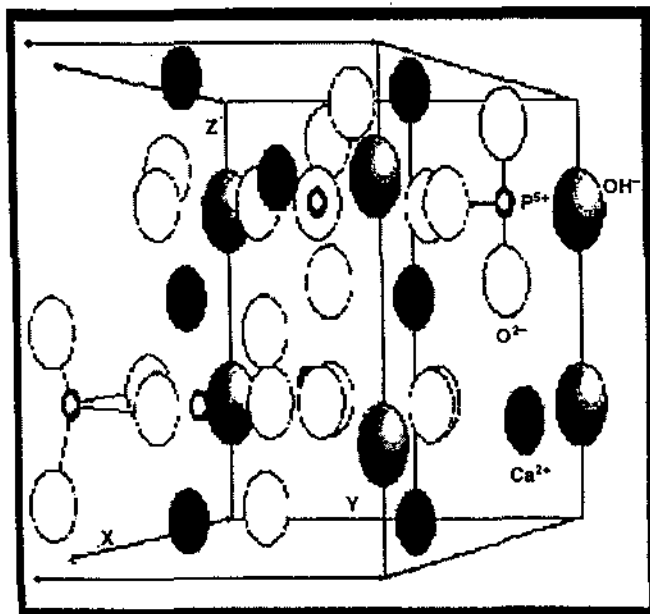


Fig. 6 – Crystal structure of stoichiometric HAp (Ca / P molar ratio : 1.67, Ca / P weight ratio : 2.151, crystal structure : hexagonal, space group : $P6_3/m$, cell parameters : $a = 9.424 \text{ \AA}$, $c = 6.879 \text{ \AA}$, theoretical density : 3.153 g.cm^{-3}).

bearing applications, ceramics should consist of fine grains because, according to the well-known Hall-Petch formula,⁴⁸ mechanical strength increases with decreasing grain size. Dense ceramics can be produced by pressing or slip casting followed by pressure-less sintering or hot uniaxial or isostatic pressing.⁴⁹⁻⁵³ In this, the density of the ceramics is $\sim 3.16 \text{ g.cm}^{-3}$.³³ Addition of 5% Na_3PO_4 has been shown to reduce the sintering temperature necessary for preparation of dense HAp ceramics by about 50°C. The use of bioglass (2.6 mol% P_2O_5 , 26.9% CaO, 24.0 mol% Na_2O , 46.1 mol% SiO_2) as a sintering aid has made it possible not only to improve mechanical properties of HAp ceramics but also their behaviour in biological environments.⁵⁴

Generally, the porous ceramics are produced by burning out organic pore formers (polyurethane sponges). Porosities of 50-60% in these items are achievable when sodium dodecylbenzene sulphonate along with about 80% glycine or agar³³ is used. Pore morphology is critical to the osteointegration process. Cylindrical channel pores up to 500 μm diameter and more than 5 mm in length are produced⁴⁹ by burning out pore formers. At physiological temperature, porous ceramics having a low strength can be produced without sintering.⁵⁵ The compressive (2-100 MPa) and bending strength (2-11 MPa) of the material drop with increasing porosity and are kept in the range 2-100 MPa and 2-12 MPa respectively depending on their application area. However, fibrous porous ceramics with improved strength can be produced following various methods,^{49, 56, 57} e.g. (a) sintering of HAp fibres or hydrothermal treatment of α -TCP, (b) dynamic densification of calcium orthophosphate and β -calcium meta-phosphate fibres etc, though the mechanical properties of the materials prepared by these procedures are below necessary level.

The granulation techniques generally adopted can be classified as follows:⁵⁸

(a) powder agglomeration in presence of a liquid phase, followed by pelletizing and consolidation of the agglomerates upon removal of the liquid phase

(b) vapour deposition with the formation of solid granules

(c) chemical reaction in a vapour-liquid mixture

(d) pressing of a solid phase, followed by grinding into granules of desired size

(e) spraying of a liquid phase followed by crystallization upon drying or cooling etc.

The granulation efficiency depends on the mechanism of the process. In the last method, an anhydrous melt is sprayed to produce approximately monosized drops which then crystallize on cooling in an inert medium such as water, oil or liquid nitrogen. Komlev *et al.*^{59, 60} used gelatin as a binder for good bonding between the powder particles. A HAp suspension in aqueous gelatin solution was dispersed in an inert liquid (vegetable oil). Due to surface tension, the resulting granules had a spherical shape, preferable for avoiding inflammatory processes and achieving osteointegration. HAp granules with a size range of 50 to 2000 μm can be obtained for commercial grades, e.g. Interpore 200 (425-1000 μm), Pro Osteon (1-9 mm) and Osteogen (500-1000 μm).

In surgery, both dense and porous HAp ceramics are used depending on requirements of bearing strength of the implants. The various clinical, dental and medical applications of dense HAp (39.68 wt% Ca, 18.45 wt% P, Ca:P wt ratio 2.151, Ca : P molar ratio 1.667) are mainly : (a) repair of bony defects in dental and orthopaedic applications,⁶² (b) immediate tooth root replacement,⁶³ (c) adjuvant to the placement of metal implants³² and (d) enhancement of guided tissue regeneration etc.⁶⁴ Porous ceramics have low strength and therefore, are suitable for implantation into tissues which experience no substantial stresses (middle ear and some maxillofacial applications) and for local drug delivery. Pores in implants are necessary for osteointegration, a process which depends on the pore size, volume and interconnectivity. The minimum pore size for bone in-growth into the implants is 100 to 135 μm to ensure blood supply to contact surfaces and tissue in-growth and fixation.⁶⁵⁻⁶⁷ Smaller pores favour protein adsorption and adhesion of osteogenic cells. So, a bimodal pore-size distribution in porous ceramics is necessary.

There are different forms of porous HAp commercially known as HA200 and HA500, which have undergone major clinical trial in maxillofacial and orthopaedic surgery. Long bone reconstructions using HA500 followed by stabilization with plate and screw fixation are done in case of some traumatic defects like road accident, gunshot injury etc. In restorative surgery also granules are used in treating parodontopathy (local and generalized, moderate and acute parodontitis and idiopathic parodontopathy accompanying insulin-independent diabetes mellitus), periodontal, follicular and residual maxillary cysts. In implantable drug delivery systems, presence of a large number of small interconnected pores and the small diffusion coefficient of the drug in the porous HAp granular matrix owing to the capillary action⁶⁸ lead to the stabilization of the drug concentration at the desired level for a targeted time period. The use of CAD / CAM (computer aided design / computer aided manufacturing) systems is also emerging in cases where medical interventions favour the application of an anatomic custom-made implant. The anatomic shapes of degenerated / damaged human bone system (marrow cavity etc) can be interpreted and identified on the basis of computer tomography (CT) data, which can be digitized and transferred to a CAD / CAM model. This possibility allows the surgeons to perform a mock operation to perfect the process prior to the actual operation and take the final decision on selection of prosthesis from the standard set. Further, by adopting rapid prototyping route through selective laser sintering efforts are being made to develop bioactive patient specific porous prosthesis as per the surgeons' needs which would decrease the operation time and in turn, the risk of the operation.

HAp powder of high purity and stoichiometric (CaO 55.60 mass% and P_2O_5 41.52 mass%) nature was synthesized by chemical precipitation method at CGCRI, Kolkata having a median particle size of 0.47 μm and a size distribution of 10-0.2 μm . At a pressure of 120 MPa, uniaxial compaction of the powder alone led to the formation of the dense granules whereas presence of pore-forming agents

formed the porous granules. Both the above specimens were sintered at 1250°C. The dense granules (relative intensity 98.7%) exhibited a fine-grained microstructure (Fig. 7) and the porous variety (50% open porosity) showed pore size distribution in the range of 1.7 to 0.2 µm. These ceramic materials were examined for their efficacy as bone substitutes in filling traumatic or pathological bone defects. The patients aged 2, 52 and 54 years were implanted with the porous HAp granules for bone tumour / fracture. Both the young and the older patients were found to have satisfactory progress in the fracture union with increase in radiographic density at the ceramic implant sites.⁶⁹ There were no toxic effects, and evidence of bone formation around HAp granules with good incorporation into the host bone was noticed. These radiographic results are consistent with those other studies of fracture.⁷⁰

In continuation to the above application areas, CGCRI, Kolkata and others⁵ have developed porous synthetic hydroxyapatite-based integrated ocular implants for application in the field of ophthalmology. First effort to develop artificial orbital implants was initiated in the late 19th century basically to fill-up the void left in the orbital socket after the removal of the infected / diseased eye through evisceration or enucleation surgery. For this cosmetic rehabilitation, different materials were tried which were slowly discarded for various disadvantages. A history of this development activity is outlined in Table III.

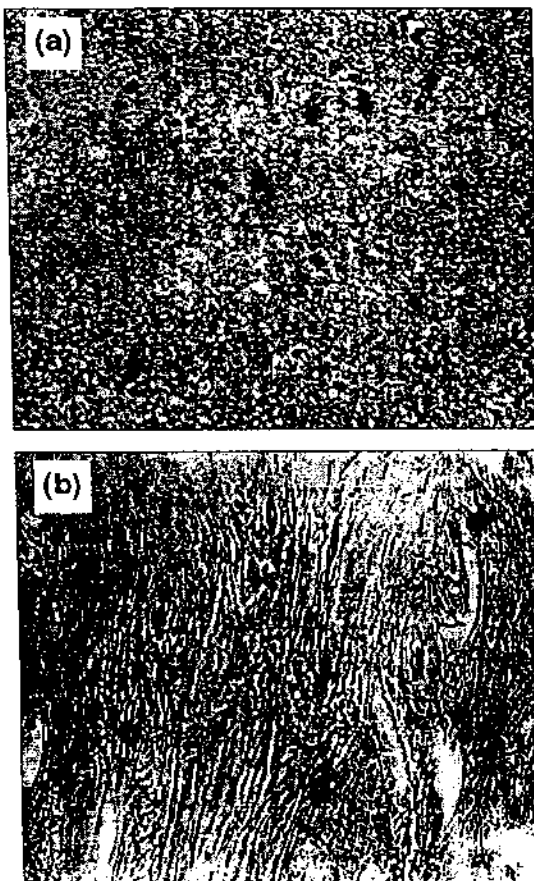


Fig. 7 – (a) Optical micrograph of dense, thermally etched HAp ceramic and (b) histological section showing bone ingrowth at 10 weeks.

Table III : Yearwise development of artificial orbital implants

Era	Material	Comments
Before 19th century	Metal	
1884	Hollow glass sphere (P. H. Muhle) • Gold, • Cartilage, • Xenogeneic animal eyes, • Silver, • Aluminium, • Silicone and • Glass beads	Unable to relieve the chronic downward pressure on the lower lead Fully buried in the orbit
1941	Acrylic based (A. D. Ruedemann)	• Partially exposed and partially buried • Manufactured before each operation • Secondary strabismus procedures required to correct late problems
1947	Prosthesis comprising an implant with a peg to completely support the weight of the artificial eye and transfer all its latent movement to the eye	High rates of infection
1976	Implants having interaction with an externally placed contact lens type artificial eye through pegs, pins or screens (H. P. Gougelmann)	• Good motility • However, prone to infection and extrusion
1989 onwards	Porous crystalline hydroxyapatite from coral	• Fibro-vascular in-growth • Providing resistance to infection, migration and extrusion • But rugged surface

Hydroxyapatite based artificial eyeball was designed and developed with the purpose of not only filling the orbital cavity volume to prevent deformation of the eye but also to provide movement of the fellow eye to improve cosmetic rehabilitation of the patient.⁷¹ Figure 8 depicts the design of the actual implant along with one such patient inserted with the implant. Presently, clinical trials of the indigenous implant in human patients have been undertaken at various medical institutions like All India Institute of Medical Sciences and Maulana Azad Medical College, New Delhi, Shankar Netrafaya, Chennai, Sarojini Devi Eye Hospital, Hyderabad and Eye Care and Research Centre, Kolkata. Nearly 40 human patients have undergone eyeball implantation without any complication till date. It has been found in all the patients that the artificial eye was with adequate motility and mimicked the other eye for both horizontal and vertical movements.⁵ Periodic MRI (magnetic resonance imaging) after 4, 6 and 8 months of the surgery revealed the location and degree of fibro-vascularization. The images of gadolinium contrast have exhibited that early peripheral activities start within 4 months whereas 70% of the fibro-vascularization is completed within 6-8 months in

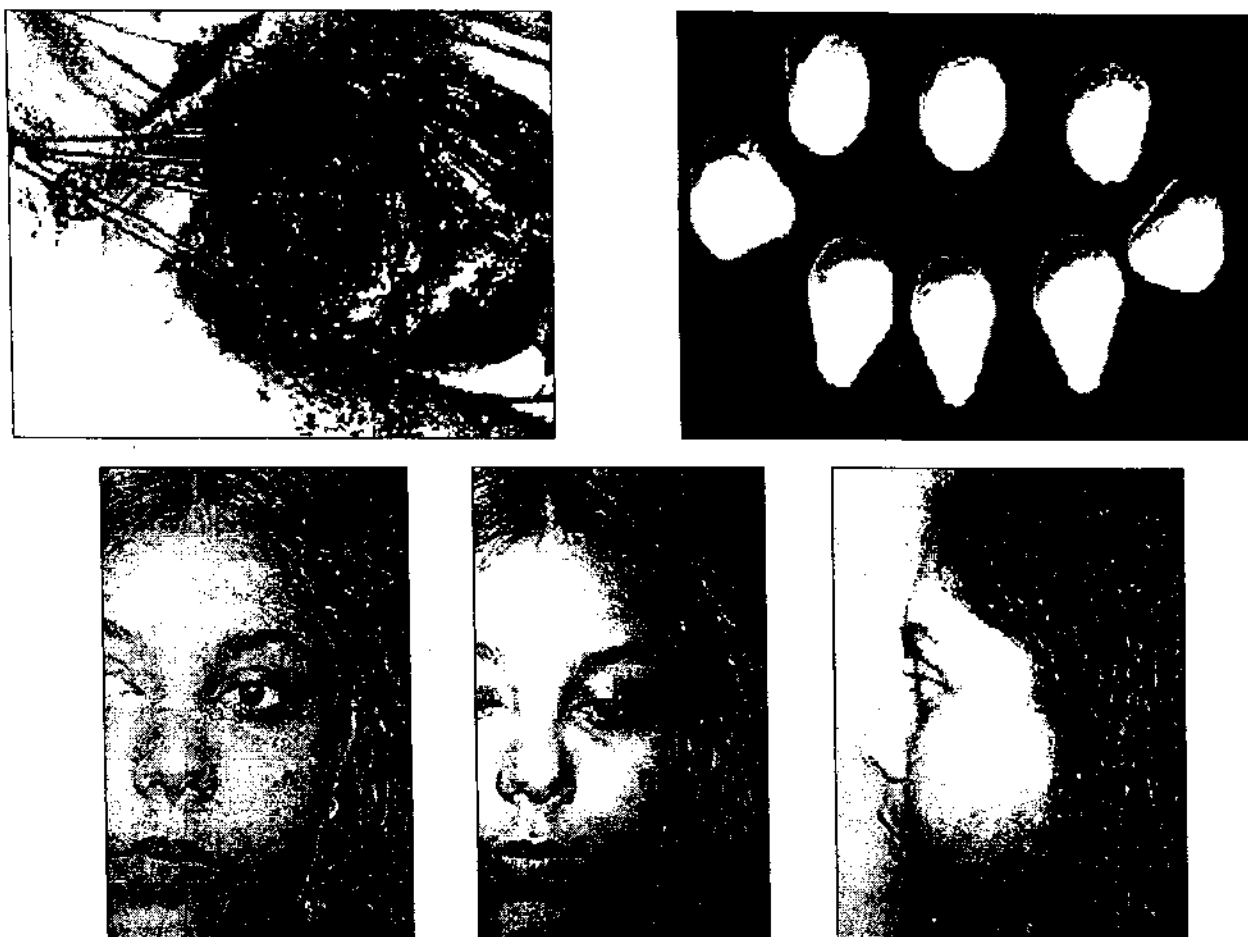


Fig. 8 – Design of the hydroxyapatite based integrated orbital implant developed at CGCRI along with one such patient inserted with the implant showing the movement of her artificial eye.

the centrally located implants.

Another newer application area of hydroxyapatite (HAp) is coating on implants for cement-less fixation. Hydroxyapatite coatings are osteo-conductive in nature, increase the kinetics of tissue in-growth and enhance the strength of the interface. HAp coated stems have been shown to have less micro-motion and subsidence than porous coated and cemented stems. Concerns with regard to HAp delamination and third body wear have not materialized with thin dense plasma-sprayed coatings. The results demonstrate excellent lasting fixation to a grit blasted tapered titanium stem with a dense highly crystalline pure proximal HAp coating. These stems have performed well in young and active patient population and have already become popular within the orthopaedic surgeons. The bioceramic coating on porous metal surfaces for fixation of orthopaedic prostheses in the osseous surrounding may be achieved by various means,^{6, 26, 31} of which plasma-sprayed coatings are generally preferred.⁷² This method provides substantial early stage interfacial bond strength which in turn ensures rigid fixation of the implants (coating thickness being ~50 µm). Indigenous activity in this field is also led by CGCRI and the programme is being pursued in collaboration with IIT, Kharagpur and M/s INOR Orthopedics Ltd, Mumbai. This research activity is aimed to develop plasma-

sprayed bioactive coatings on different implant materials for their cement-less fixation which are being characterized in detail.⁵ HAp / bioglass-coated dental implants have also been developed and implanted in human subjects and the preliminary post operative results are encouraging.⁵

However, there are some potential problems associated with cement-less prosthesis in bone in-growth fixation, which are as follows:

- According to Wolff's law of bone remodelling, load is concentrated at the area of rigid fixation and would bypass a large area resulting in stress shielded bone resorption.
- During revision surgery, removal of such a stem without destruction of bone would be difficult.
- Varying degrees of heat treatment required for sintering process of porous surfaces substantially reduces the fatigue strength of the implant due to various microstructural as well as other transformations. In addition, porous layer substantially increases the surface area of the metal, resulting in the acceleration of the corrosion process, which may lead to prosthesis loosening and metal ion releasing. Accumulated metal ion may cause adverse systemic effect.

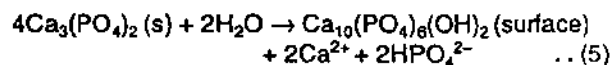
Therefore, at present, to eliminate the problems associated with heat treatment, biomimetic coating has emerged as a promising technique that overcomes some of the intrinsic drawbacks of the plasma-spraying method. It also

rates a dense, uniform and homogeneous hydroxyapatite coating on metal substrates at room temperature. The coating thickness varies in the range of 30-50 μm . In this, bioactive metal implants (Ti metal, Ti metal alloys, stainless steel, Co-Cr alloys) are soaked into a solution called simulated body fluid (SBF) at physiological pH (7.4) and at room temperature (37°C) conditions. The SBF has similar ionic (inorganic) concentrations as human blood plasma.⁷³ Under such experimental conditions it is possible to coat heat-sensitive materials, e.g. polymers and to cover complex shaped materials, e.g. porous implants. Also, this technique allows the covering of implants with new Ca-P phases⁷⁴ that could not be produced at high temperatures. Depending on the crystal size of the precipitating phase, the biomimetic coating have different structures, dissolution behaviour⁷⁵ and phase composition. These specific characteristics of the method can be highly beneficial for bone formation as compared with the HAp-plasma-sprayed coating. The time consumption factor in this process is shortened / overcome by chemical treatment of the substrate / increasing the concentration of the SBF solution.

In India, also CSIR (Council of Scientific and Industrial Research), New Delhi has initiated a network project involving CGCRI, Kolkata and National Metallurgical Laboratory (NML), Jamshedpur to develop HAp coating on metal substrates adopting biomimetic method. The work is in progress and Fig. 9 depicts some of the early results.⁷⁶

With a nominal chemical composition of $\text{Ca}_3(\text{PO}_4)_2$, β -TCP has a Ca : P ratio of 1.5. There are four polymorphs of anhydrous TCP — α - $\text{Ca}_3(\text{PO}_4)_2$ (α -TCP), the stable phase between 1120° and 1470°C but metastable below 1120°C; α' -TCP, stable above 1470°C; β - $\text{Ca}_3(\text{PO}_4)_2$ (β -TCP), stable below 1120°C; and β' -TCP, stable at high pressures.⁷⁷ Structures of α - and β -TCP have been classified as glaserite-type, named after the mineral glaserite ($\text{K}_3\text{Na}(\text{SO}_4)_2$), while β -TCP crystallizes in the rhombohedral space group $R\bar{3}c$ with unit cell parameters $a = 10.439(1) \text{ \AA}$, $c = 37.375 \text{ \AA}$, $Z = 21$ (hexagonal setting).⁷⁸ The structure of β -TCP has been described as a distorted version of the $\text{Ba}_3(\text{PO}_4)_2$ structure

which has identical columns of PO_4 -Ba-Ba-Ba- PO_4 in a hexagonal arrangement. Due in part to its crystalline structure, biodegradation rate of TCP is much greater than that of HAp. Though the exact mechanism of biodegradation is not clear, it has been reported¹ that β -TCP dissolves *in situ* in acidic environment or cellular breakdown by macrophages take place among the osteoclast-like cells attached to the implanted TCP. Consequently, the function of these totally biodegradable (resorbable) biomaterials is merely to serve as a scaffolding / filler of space, thereby permitting tissue infiltration and replacement. This leads to elimination of a second surgical procedure as is evident in autologous bone grafts, though there is a serious reduction in strength that occurs during the resorption process. The chemical interaction of the implanted TCP with the body fluid to form HAp may be given as:



This reaction decreases the pH of the solution adjacent to the implant which in turn, increases the solubility of TCP. Therefore, after implantation, TCP progressively degrades and is slowly replaced with natural tissues. It is important that it leads to regeneration of tissues instead of their replacement and thus renders good interfacial stability. Though an ideal implant material, some limitations restrict further extensive use of TCP for clinical applications.^{5, 79}

As indicated above, another potential application area of the porous HAp and TCP blocks is in the form of matrix for sustained release of anticancerous drugs, e.g. cisplatinum⁸⁰ and methotrexate.⁸¹ A concentration of 0.1 to 1 $\mu\text{g.mL}^{-1}$ *in vitro*, effective against tumour cells, is delivered in a sustained manner for over 12 days in methotrexate loaded ceramic matrix drug. Porous blocks of HAp are also studied for sustained release of antibiotics, e.g. gentamycin sulphate, cefoperazone sodium⁸² etc. Ceramic delivery systems with TCP and HAp have been developed for azidothymidine (AZT) in AIDS patients, by compressing the mixtures at low load of 300 lbs.⁸³ A coating of vitamin

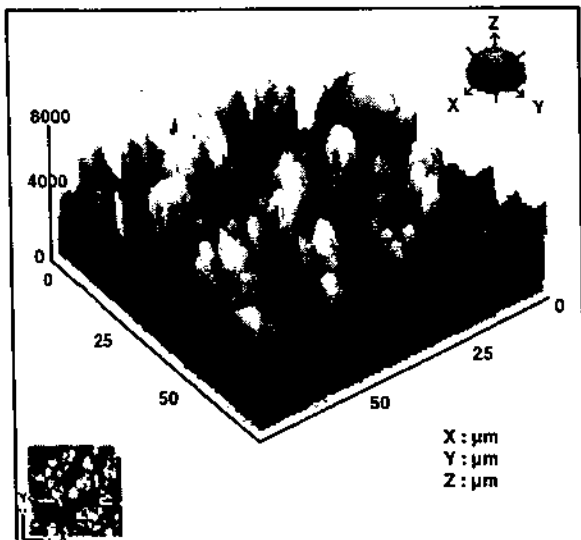


Fig. 9 – The AFM and SEM microstructures of the biomimetic coating (HAp) on Ti6Al4V substrate, developed at CGCRI, Kolkata.

E oil has lowered the release rate *in vivo* when implanted in Sprague Dawey rats. HAP microspheres with an irregular porosity of 1 to 30 μm and pore volume of $0.3 \text{ mL}\cdot\text{g}^{-1}$ have been used for protein and peptide drug delivery applications. These have been loaded with insulin and coated with polyethylene vinyl alcohol for sustained release.⁶⁴

In a study with the TCP ceramic capsules it has been seen that capsules prepared from small particle size powders are denser and the release rate is slower. Compressing the homogeneous material of TCP ceramic capsules with amino acids incorporated at 500 kg load the capsule delivers progesterone in a sustained manner. Here, the release is dependent on the physicochemical characteristics of the amino acid used.⁶⁵ Other than HAP and TCP, calcium phosphate cements, nontoxic and biocompatible ALCAP (aluminocalcium phosphorus oxide), ZCAP (zinc calcium phosphorous oxide)⁶⁶ have also been studied as drug delivery devices. ZCAP, when used as matrix for diabetic patients releases zinc in traces that helps wound healing,⁶⁷ ALCAP ceramic capsules have been investigated *in vitro* for sustained delivery of azidothymidine (for AIDS patients) that has severe side effects including toxic effect on bone marrow.⁶⁸ *In vitro* drug release from a self-setting bioactive calcium phosphate cement containing the anticancer agent, 6-mercaptopurine (6-MP), was investigated as a model compound. *In vitro* drug release profiles from loaded cement pellets (0.9 to 4.8% by wt) in phosphate buffer at pH 7.4 and 37°C followed Higuchi equation.⁶⁹

The major advantages of ceramic drug delivery vehicles are: (a) targeted local delivery of drug at a constant rate, (b) less drug required to treat the disease state, (c) minimization of the possible side effects, and (d) enhanced efficacy of the treatment. Protein drugs may become denatured within the polymeric matrix⁶⁸ due to interaction between the drug and the matrix, resulting in loss in biological activity and changes in immunogenicity. So, the above biocompatible, resorbable and porous ceramics serve as good candidates for drug delivery applications.⁶⁸ Moreover, these delivery systems can protect the drugs that are unstable *in vivo* and require frequent dosing intervals. Though the cost/benefit ratios of these drugs are too high, in future, it is expected that low cost implantable systems would be developed for delivery of anticoagulants, anticancerous drugs, insulins, vaccines and steroids etc which would revolutionize the treatment procedure.

Bioactive Glasses and Glass-Ceramics

Bioactive glasses are manufactured by conventional glass manufacturing methods.¹ The choice of raw materials here can affect the properties of the glass which are tailorable as per their application area. Basically, the most well studied composition of these materials is 45 wt% SiO_2 , 24.5 wt% Na_2O , 24.5 wt% CaO , with a constant 6 wt% of P_2O_5 . Under the trade names 45S5, 45S5.4F etc, these glasses, termed as 'bioglasses', are known to form stable bonding (chemical bonding of hydroxyapatite, embedding collagen fibres and bone cells) to bone when implanted *in vivo* for repair and reconstruction of diseased and damaged tissues, especially hard tissue. The ternary SiO_2

Na_2O - CaO diagram (Fig. 10) represents the bioactive-bonding-boundary compositions. At the centre, the composition A is most suitable for the rapid formation of apatite and hence termed as 'bioactive region'. 45S5, 45S5.4F, 55S4.3, Ceravital (see later), A/W glass-ceramics (P_2O_5 , 6.2 wt%) all belong to this region which also comprises region E (dashed line) meant for bioactive glasses / glass-ceramics undergoing soft tissue bonding specifically. Earlier, it was believed that P_2O_5 is an essential constituent of glass to make it bioactive, though, it has been shown presently that the minimal melt-derived glass compositional system for bioactivity is CaO - SiO_2 (compositional limit - 60 mol%) (Kokubo *et al.*) and for gel-derived glasses, it is SiO_2 - Na_2O - CaO (compositional limit - 85 mol%) (Li *et al.*). The role of phosphate in the glass is to aid in the nucleation of calcium phosphate phase on the surface of the glass substrate. Compositions at region B are 'bioinert' as they are SiO_2 -rich and lead to the formation of a non-adherent fibrous capsule. Region C with poor CaO content comprises the resorbable glass / glass-ceramics.

In all known bioactive implants including bioactive glass and glass-ceramics, it is essential that a layer of biologically active hydroxycarbonate apatite (HCA) must form on the surface to form a bond with the surrounding tissues. A sequence of chemical reactions like leaching and dissolution is followed by precipitation of an amorphous calcium-phosphate (CaP) rich layer on the surface that later crystallizes to a HCA structure slowly by incorporating carbonate ions from the body fluid.¹⁵ Rapid growth of HCA agglomerates incorporates collagen, monopolysaccharides and glycoproteins consequently into the active surface layer forming an organic-inorganic composite.⁹⁰ Within a week, the mineralizing bone appears at the interface of the more

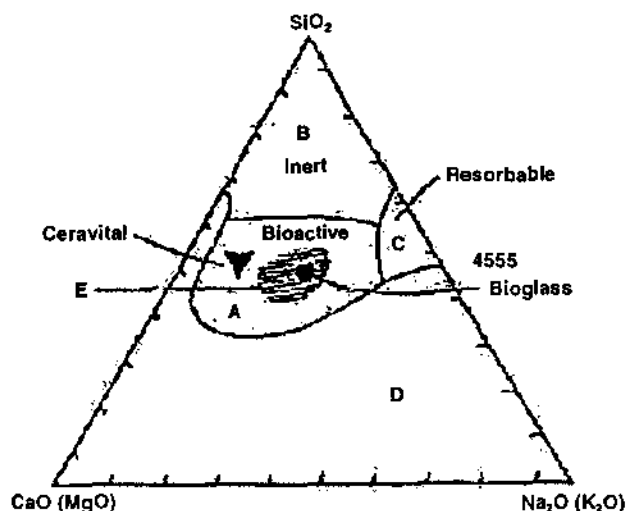


Fig. 10 - The ternary SiO_2 - Na_2O - CaO diagram: Compositional dependence (in wt%) of bone bonding and soft tissue bonding of bioactive glasses and glass-ceramics. All compositions in region A are bioactive and bond to bone. They have a constant 6 wt% of P_2O_5 . A/W glass-ceramic has higher P_2O_5 content. Compositions in region B are bioinert and lead to formation of a non-adherent fibrous capsule. Compositions in region C are resorbable. Region D is restricted by technical factors. Region E (soft tissue bonding) is inside the dashed line where the index of bioactivity, IB , is >5 .

reactive bioactive glass substrate and by four weeks, the interface is completely bonded to bone without any intervening fibrous tissues.¹⁵ Studies on bone-bonding to bioactive glasses and glass-ceramics by various research groups (Florida group, Kyoto group, Andersson group, etc) exhibited very high interfacial strength values using different mechanical test methods. Bioglass (45S5) implants in rat tibia ($4 \times 4 \times 1 \text{ mm}^3$) were tested for pull-out force after various periods of implantation time. After 30 days, 100% of these showed a pull-out force of ~ 30 N. In comparison, control implants of stainless steel and alumina showed no bonding and pull-out forces of less than 10 N. So, it is evident that the bonding ability and the bond strength of bioactive glasses (45S5) to both hard and soft tissues of our musculoskeletal system are distinctly higher than other bioactive implants (HAp) that do not bond to soft tissues.

Some of the important characteristics of the bioactive glasses used clinically are as follows:

- (a) a rapid rate of surface reaction that leads to fast tissue bonding *in vivo*,
 - (b) a low elastic modulus of 30-35 GPa which is close to that of a cortical bone,
 - (c) mechanical weakness and low fracture toughness due to an amorphous two-dimensional glass network,
 - (d) low tensile bending strength (40-60 MPa).
- The last two properties make them unsuitable for load

bearing applications, though they can be used as coating, buried implants, low-loaded / compressively loaded devices, in form of powders / bioactive phase in composites. Strength of bioglasses can be increased by preparation of a fine-grained apatite-containing glass-ceramic, comprising 10-15 wt% P_2O_5 in a high- SiO_2 and high- CaO glass, termed as 'Ceravital'.⁹¹ Another bioactive glass-ceramic, termed as A/W (Apatite, Wollastonite, commercial name - Cerabone) that consists of 38 wt% apatite, 34 wt% wollastonite and 28 wt% residual glassy phase (MgO 16.6 wt%, CaO 24.2 wt% and SiO_2 59.2 wt%) has an especially important load bearing clinical application in the replacement of vertebrae (Kokubo et al, 1982).⁹²⁻⁹⁶ Previously, autograft or allograft in combination with metals, PMMA (polymethyl methacrylate) bone cement or Al_2O_3 ceramics were attempted for reconstruction of extensively damaged vertebral column (Fig. 11). All these were often unsatisfactory because of limited availability / non-bonding resulting in loosening and dislocation of the implant during use.^{97, 98} The high compressive and bending strengths (1080 MPa and 215 MPa respectively), fracture toughness ($2.0 \text{ MPa}^{1/2}$),¹ high interfacial bond strength to bone and the excellent resistance to degradation when applied *in vivo* have established the utility of the material to replace surgically removed vertebrae since 1983. It is a crack and pore free, dense, homogeneous glass-ceramic made by densifying $5 \mu\text{m}$ sized glass powders into desired shapes followed by

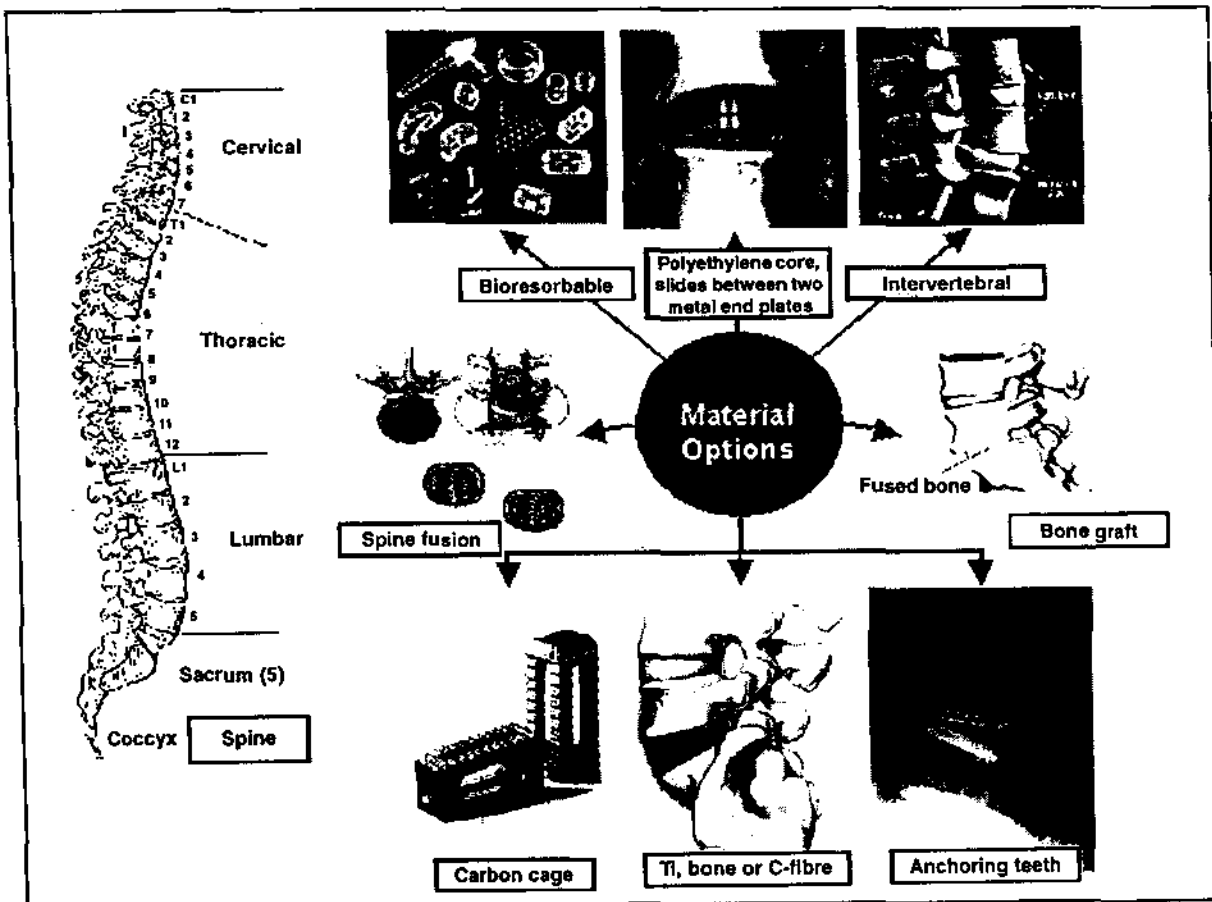


Fig. 11 - Glass-ceramic and composite materials used as vertebral implants.

precipitating oxyfluorapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{O}, \text{F}_2)$) and wollastonite (CaO-SiO_2) phases in the matrix.

At an intermediate stage, after extraction of teeth and prior to fitting of dentures, preservation of jaw-bone of patients is essential and is done by endosseous ridge maintenance implant (ERMI, Stanley *et al.*).^{99, 100} Another clinical problem called 'conductive hearing loss',¹⁰¹⁻¹⁰⁴ caused by chronic infection of ossicles (small bones of the middle ear) is met by 'ossicular prosthesis', using 45S5 bioactive implant (Fig. 12). Here, the bioglasses bond both with the collagen of the eardrum and the bones of the stapes footplate, thereby anchoring the implant firmly on both ends. This prevents extrusion possibility and the micro-motion of the implant-tissue interface that occurs when bioinert implants are used. Also, there is no growth of fibrous tissue to impair the sound transmission, so the sound conduction is excellent in a patient.¹⁰⁴ Because of disadvantages of autograft materials and homograft implants, alloplastic materials (biocompatible, bioinert or bioactive) have replaced the former in ossicular prostheses. Stainless steel, titanium and gold are biocompatible materials used for ossicular reconstruction. The prototype bioinert material, dense aluminium oxide does not release any detectable trace substances, when used in ossicular implants. This material was popular in Germany and Japan and the implant can fit the undersurface of the tympanic membrane without cartilage coverage. The high surface energy and

extremely low surface roughness result in fast and strong adsorption of biological molecules in alumina. These adsorbed molecules limit the direct contact of the articulating solid surface. Plester and Jahnke¹⁰⁵ have developed partial ossicular bone replacements made of alumina. It showed better performance in comparison to polymeric components. The bioactive implants (HAp, bioglass) react favourably with the body tissues to promote soft tissue attachment. It is a direct chemical bond to the surface of the material unlike the mechanical attachment that occurs with bioinert and biocompatible materials and as a consequence it is expected to offer better property and longer life.

Composites

It was Hulbert¹ who reasoned that bioactive metals when implanted *in vivo* were not in their highest oxidation states, and so might undergo ionization that might produce some degree of effect in the body. On the contrary, for a number of biomedical applications, ceramics alone, either bioactive or inert, could not meet the diverse requirements of safe and effective *in vivo* functioning. This turned attention towards composite materials, which could take advantage of the desirable properties of each of the constituent materials. Table IV lists the material combinations of the composites of various natures that are already in use and their possible applications.

Our cortical bone at the ultrastructural level is a

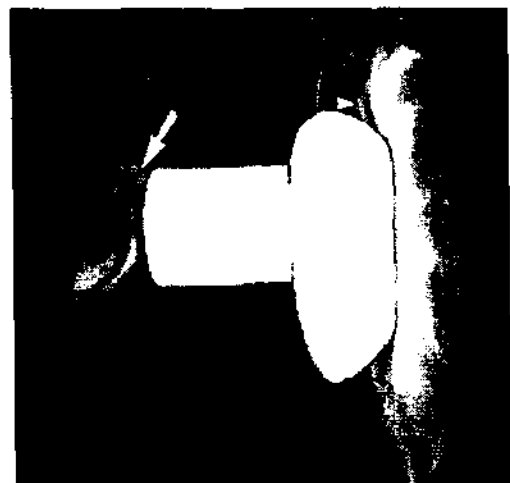
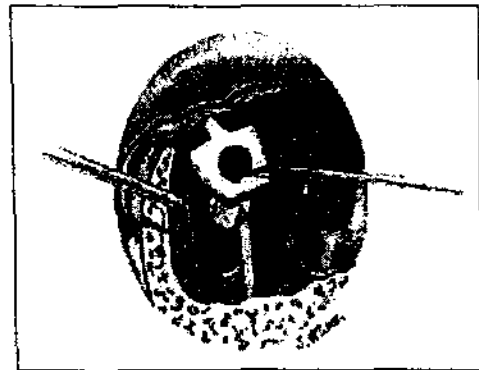
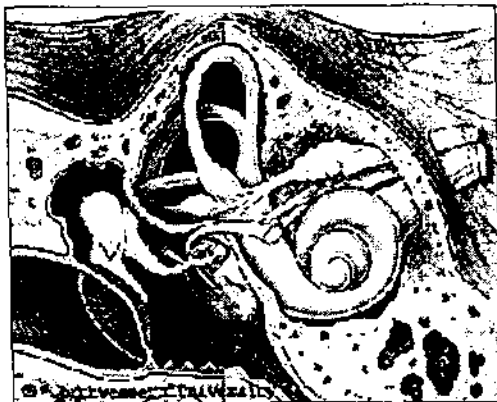


Fig. 12 - Ossicular prosthesis using 45S5 bioglass.

Table IV : Composites containing ceramics for medical applications

Ceramic material	Partner material	Composite structure	Application
Alumina	Stainless steel, titanium	Coating	Tissue in-growth
Bioglass	Stainless steel, titanium	Coating	Bone bonding
Bioglass	PMMA (poly methyl methacrylate)	Cement	Chemical bond to bone
HAp	Cancellous bone	Mixture	Alveolar ridge augmentation
HAp	PLA (Polylactic acid)	Elastomer	Tissue in-growth
Carbon	PLA	Laminate	Tendons, ligaments
Carbon	PLA	Laminate	Bone plate

hydroxyapatite (HAp) reinforced collagen composite.¹ The anisotropic deformation and fracture characteristics of the cortical bone lead to high critical stress and strain intensity and Young's modulus in the range 7-25 GPa. Most bioceramic materials are stiffer than bone and exhibit poor fracture toughness. Therefore some additional biocompatible materials with lower elastic modulus are often added to HAp ceramics to form a composite to enhance strength and reduce brittleness of the material. Of these, polyethylene based composites containing 40% HAp offers Young's modulus of 1-8 GPa, close to that of living bone. However, polyethylene is bioinert and this weakens the bonding between the implant and the bone tissue.

The HAp-collagen composite can be produced by mixing HAp powder and collagen solution followed by curing the mixture under UV radiation / pressing at 40°C under a pressure of 200 MPa. This results in a low-strength material with tensile strength of 6.5 GPa and Young's modulus of 2 GPa. A new approach has been introduced by Orlovskii *et. al.*⁵⁴ to incorporate desired quantity of polymer into a continuous ceramic skeleton that leads to much improved biological and mechanical properties in comparison to the conventional polymer-ceramic composites. In recent years, a wide research effort has been devoted to develop new ceramic-matrix composites reinforced with particles, fibres, metals, apart from HAp-polymer composites like HAp-polyethylene,¹⁰⁶ HAp-collagen,¹⁰⁷ HAp-poly lactide,¹⁰⁸ HAp-PMMA¹⁰⁹ and many others.

Other Devices / Implants with Bioceramic Hardwares

Ceramic materials have been given a lot of attention as biomedical implants since long ago as they possess some highly desirable characteristics for some specific applications. Other than their extensive medical application in the field of orthopaedics, they have been used in dentistry for their inertness to the body fluids, high compressive strength and resemblance to natural teeth. Also, for blood interfacing applications like heart valves, the high specific strength of carbon fibres and their biocompatibility has been utilized. For artificial tendon and ligament replacements composite

ceramic materials comprising carbon fibres as reinforcing component are applied in tensile loading applications.

Porous resorbable aluminocalcium phosphorus oxide (ALCAP) ceramic capsules have been used effectively to deliver steroids at constant rates for a long period of time.¹¹⁰ Such drug delivery systems are extremely useful in cases where (a) the drugs are degraded on ingestion in the digestive tract, thereby greatly reducing or eliminating the intended effect of the drug, (b) slow release of the drug is intended in a sustained manner over a prolonged period of time. Traditionally, the patients having spermatogenesis are treated by the steroid androgen, either orally or by injection.¹¹⁰ In this, large amount of hormones have to be administered to overcome poor absorption and degradation in the G-I tract problems.^{111,112} To overcome such problems, implantation of ALCAP ceramic devices (intraperitoneally) containing 40-80 mg of testosterone (T), dihydrotestosterone (DHT), danazol (D) or combinations of these androgens have been observed to maintain normal spermatogenesis by providing the extra amount of steroid needed for the same.¹¹³ Thus, the ceramic steroid delivery system regulates the male spermatogenesis in a reversible manner without causing undesirable side effects.

Retinal Implants

The physiology of vision is very complex and despite enormous efforts and advances in clinical treatment of eye-diseases there is no established method to prevent / cure degenerative processes in eye, e.g. age related macula degeneration (AMD) and *retinitis pigmentosa* (RP). In this, RP is an inherited condition which involves progressive decay of the photoreceptor cells of the outer retina (the rods and cones that normally converts light into electrical impulses are damaged) though the neuronal network including optical nerve and optical ganglia may survive for an extended time period. The symptoms at first are night blindness subsequently followed by a gradual decay of the peripheral vision. This condition slowly ends up in complete blindness, as, the over-reacted rhodopsin pigment in the patients ultimately damages / kills the retinal cells. The average age at which patients become legally blind with a central visual field diameter of less than 20 degree is about 60, with a minority as less as 30. In these cases, ophthalmoscopic findings may range from normal to attenuated retinal vessels, intra-retinal pigment and waxy pallor of the optical disc in more advanced cases.

The retina in the eye converts light information into neural electrical signals, which the optic nerve transports to the visual cortex of the brain. The visual cortex decodes the neural signals into a meaningful image perception. The retina is composed of approximately 126 million photoreceptors which have sizes ranging from 2 to 3 µm. The photoreceptors provide an analogue graded potential to the attached bipolar neural cell layer which converts the electrical signal into electrical pulse train maintaining spatiotemporal information.

Scientists worldwide have devoted substantial research capacity to develop micro-technical retina implants. In USA, implantable retina stimulator,¹¹⁴ in Japan,¹¹⁵ in Australia¹¹⁶

and in Germany ¹¹⁷ artificial retina prosthesis / artificial retina / bionic eye to combat retinal dystrophies are being developed. In one approach, ultra-thin and flexible micro-photo-diode arrays (MPDA) have been developed on the amorphous silicon of thickness 1 to 5 μm ¹¹⁸ for sub-retinal implantation. Here, an amorphous silicon photoconductor is used for local light induced enabling of the stimulation current which is driven by a crystalline solar cell acting as an infrared receiver. Thus the enhancement of stimulation power is done by the additional conversion of the near infrared radiations, as, the visible light alone cannot generate a sufficiently high charge transfer to the retina cells. The thin oxide films are photo lithographically patterned into the micro-detector arrays that mimic the size and distribution of cones in human retina. The patterned array is then transferred to a dissolvable polymer carrier layer that can be surgically handled for implantation into the eye.

In another approach, micromechanical implants integrated into flexible and rigid substrates for stimulation of epiretinal and subretinal space have been fabricated. In the epiretinal project, a thin (15 μm) polyimide cable with embedded platinum conductors connects the receiver chip with the stimulator die.¹¹⁸ The flexible polyimide foil serves as a carrier and the insulation layers that hold platinum / gold / iridium based microelectrodes, conductive lines and interconnection pads.

Biostability of MPDA *in vitro* and *in vivo* exhibits dissolution of silicon oxide passivation layer¹¹⁷ within a period of 6 to 12 months and subsequent corrosion of the underlying silicon. So, this material has been replaced by stimulation microelectrode consisting of planar titanium / gold or nanoporous Ti / TiN which have been well preserved both *in vitro* and *in vivo*.

Recently, ceramic optical detectors based on photo-ferroelectric effects are being developed for direct implantation into eyes of the RP patients.¹¹⁹ These detectors solve a major problem plagued by the silicon implants. In this, the naturally porous structure of the ceramic allows nutrients to flow from the back to the front of the eye, preventing atrophication of the retina. Also, unlike silicon, a ceramic does not require encapsulation and in addition, no wire connection is required to the bipolar layer of cells neighbouring the human cones. The micro-detectors are simply placed in the sub-retinal space as an array of individual micro-detectors of the size of one twentieth of a human hair, an assemblage so small that surgeons cannot safely handle it. So, the arrays are attached to a polymer film, one millimeter by one millimeter, that is designed to be dissolved in a couple of weeks leaving the array in position on the retina. These ceramic heterostructures show excellent biocompatibility and under optical illumination can generate local photocurrent / photovoltage that excites the retinal neural circuit resulting in a signal at the optic nerve that may be translated by the cortex of the brain into a visual perception. Figure 13 depicts the retinal implants which has been conceived presently. In this case, the ultrathin layers of oxide films comprising PbLaZrTiO_3 (PLZT) and DyVO_3 (DyVO) fabricated by a high power

laser deposition process, exhibit a strong photo-response in visible range overlapping eye response from 380 to 650 nm.

Heart Valves

The heart is a vital part of the human anatomy as it functions as a pump to circulate blood throughout the body. Heart valves allow the heart to pump blood to specific locations of the body. These valves are prone to disease and malfunctioning, e.g. stenosis and incompetence. In stenosis, the heart valve does not open fully due to stiffened valve tissue, hence more work is required to push blood through the valve. An incompetent valve causes inefficient blood circulation as a result of backflow of blood in the heart. Although medication is the best alternative, prosthesis is required in some cases for normal life of the patients.

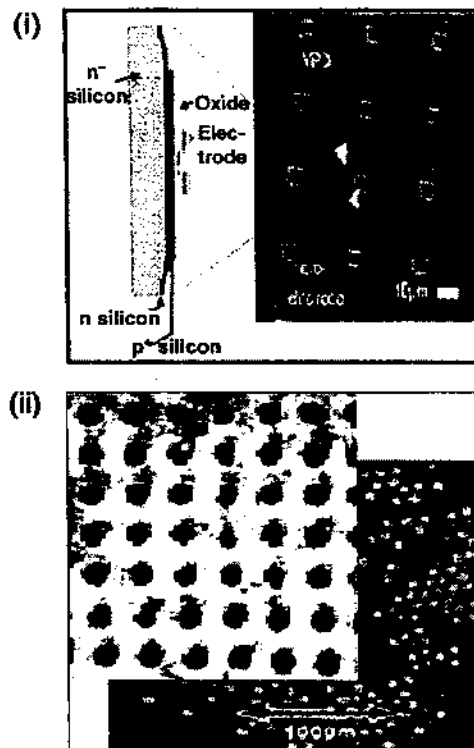
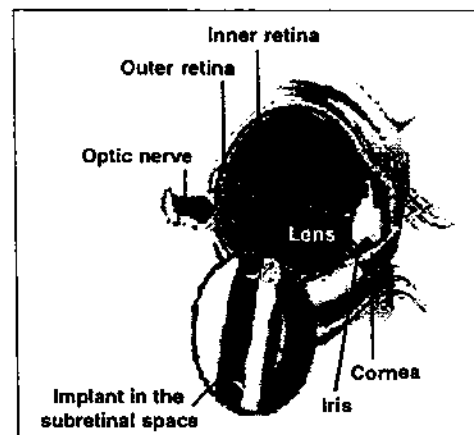


Fig. 13 – Subretinal implants : (i) microelectromechanical system (MPDA detector) (ii) ceramic optical detector.

Broadly, there are two main categories of prosthetic heart valves : (i) mechanical and (ii) bioprosthetic.

(i) The mechanical valves have excellent durability but are hindered by a tendency to coagulate blood. So, they are applied in younger patients so that they last for life-time. The first mechanical prosthetic heart valve was implanted in 1952. A wide evolution of design of these valves has taken place from simple caged valves to bileaflet valves (Fig. 14). The caged-ball valve completely blocks the central flow of blood and damages blood cells due to collision. These blood cells release blood-clotting ingredients causing the patients to take anticoagulants lifelong. Next, during 1960's, tilting-disc valves with a tilting angle of 60° and a close shut completely at a rate of 70 times/min reduced the damage to the blood cells though there was a tendency of fracture of the outlet struts on repeated ramming of the

struts by the disc. In 1979, bileaflet valves with two semi-circular carbon leaflets were designed that pivot on hinges, exhibit high strength, excellent biocompatibility and open completely parallel to the direction of the blood flow. As they do not close completely, some backflow of blood takes place, though these valves provide the closest approximation to the central flow achieved in a natural heart valve. The most commonly used materials for the fabrication of these valves are stainless steel alloys, molybdenum alloys, pyrolytic carbon for the valve housings and leaflets, silicone, teflon and polyester (dacron) for sewing rings.

(ii) Bioprosthetic heart valves have better hemodynamics, do not damage blood cells and can be subdivided into human tissue valves (homograft, transplanted from one human being to another, and autograft, transplanted from the same patient that they are implanted into) and animal

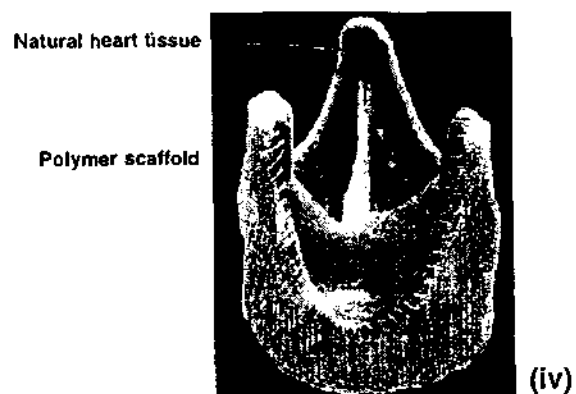
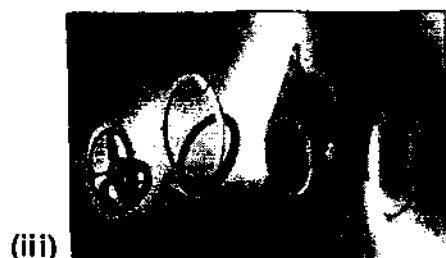
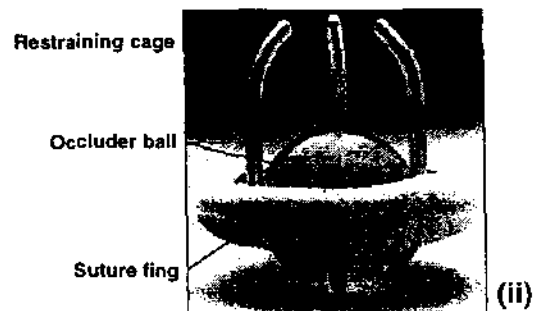
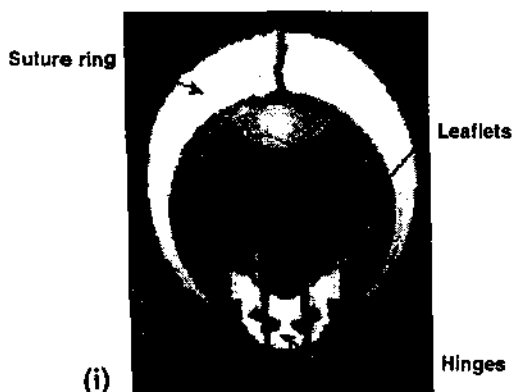
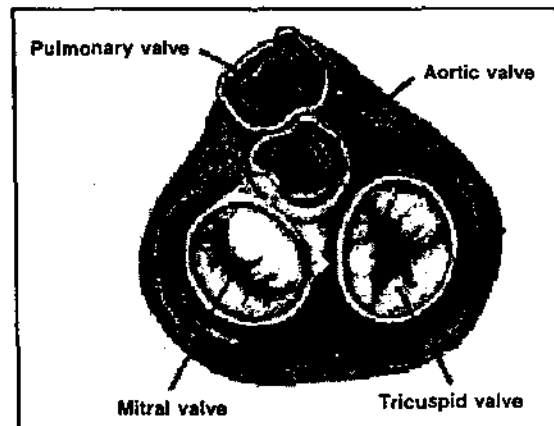
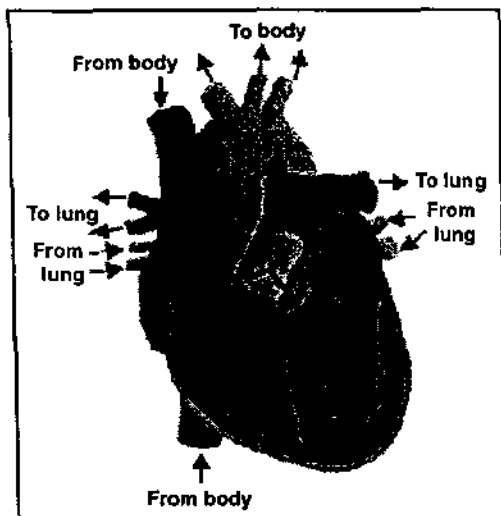


Fig. 14 – Cross-section of heart showing valve locations and pumping and circulatory functions. Mechanical heart valves showing (i) caged ball, (ii) bileaflet design, (iii) bioprosthetic heart valve and (iv) porcine valve.

tissue valves (heterograft or xenograft valves). The highest quality leaflet tissue is preserved and stiffened using glutaraldehyde (porcine / bovine pericardial tissue). Here, the valve tissue is sewn to a metal wire stent (porcine valve, Fig. 14) made of cobalt-chromium alloy. The wire is bent to form three U-shaped prongs. A dacron cloth sewing skirt is attached to the base of the wire stent, the stent themselves are also covered with cloth.

Imachi *et al.* fabricated jellyfish valve 0.2 mm thick, made of card iothane by casting. It has 12 spokes to prevent prolapse of the membrane, and is made of solution casted polyurethane and coated with cardiothane. Under specific circulation condition (pump output = 6 L.min⁻¹, inlet pressure = 4 mm Hg, outlet = 210 / 160 mm Hg, pulse rate = 100 bpm) no thrombus was formed on or around the valve membrane.¹²⁰

In another attempt, a central flow trileaflet valve has been fabricated using flexible material strong enough to withstand high stresses exerted on valve leaflets in a working heart. The composite material [EPDM (ethylene propylene diene terpolymer)-rubber (has high flex life and good abrasion resistance)], that has both flexibility and strength of a natural aortic valve (fibre-reinforced leaflets) has been used here.¹²¹

In still another attempt, self-assembled polymer monolayers that carry photoreactive groups, e.g. benzophenone unit have been used for attachment of prefabricated polymers (photochemical approach).¹²² These layers mask the toxic groups generated at the surface of the bioimplants (animal tissue valves) during a glutaraldehyde treatment needed to improve mechanical stability of these xenografts.¹²³

Vertebral Implants

The loss of bone in the spine often presents serious difficulties not seen in other areas of the body. Vast advances in fusion techniques and instrumentation have markedly facilitated the treatment of various spinal disorders. Discs are the cartilages that lie between the bony vertebral bodies of the spine; they are the most vulnerable component of a human vertebra. Since motion occurs in this area, these are considered as joints and in aging process, discs lose their water content and are degenerated. Tear occurs in the outer lining of the disc (annulus), causing degenerative disc disease (DDD) that requires artificial disc replacement. In this, a polyethylene core (Fig. 11) slides between two metal end plates that are attached to the vertebral body with anchoring teeth built along the rim of the end plates. This replaces the injured disc and the polyethylene core allows movement of the spine unlike fusion that prevents normal movement.

When a disc ruptures, it is not able to support the body weight and the space between the vertebrae narrows. This causes the nerves to be pinched, and slowly the facet joints become arthritic, get larger and develop bone spurs. This is spondylolysis that leads one vertebra to slip on other. This is a dynamic process and the disc is to be removed (by laminectomy / disectomy) to relieve pressure on the nerve. In this, spinal fusion relieves pressure on the nerve and keeps vertebrae from slipping. A fusion cage can be put either from the back or front. A BAK (Bagby and Kuslich) cage device is a hollow threaded cylinder with holes and is

made of titanium. The holes are filled with bones taken from the lamina. Bone grows through the holes to fuse the vertebrae from above and below. On the other hand, a carbon fibre cage is a composite of long carbon fibres and a polymer matrix (polyether ether ketone), designed in the shape of a trapezoidal hollow box (Fig. 14). As in the previous case, the upper and the lower surfaces of the cage are open to allow packing with bone graft and to provide a wide area of contact between the graft and the adjacent vertebra. The cage is radiolucent with one radio-opaque tantalum bead incorporated at each corner.¹²⁴

In active younger individuals, pressure on lumbar spine may be greater than what the cages can support. Also, for patients who already had back surgery, it is very difficult to create enough room for two titanium cages without risk of nerve injury. In these cases a 360° fusion is used with only one implant (Ti / bone / carbon fibre) placed between the vertebral bodies at an angle. Once the bone heals, the strength of one cage at an angle (360° fusion) has been seen to be as strong as two cages straight in.

The use of bioabsorbable implants, e.g. alpha-polyesters in current development of spinal instrumentation and surgery is widespread. Polylactide and polyglycolide, whose breakdown products are lactic and glycolic acids respectively, are familiar to the physiological milieu of the body. Van Dijk *et al.*,¹²⁵ evaluated the compression strength and mechanical properties of titanium lumbar interbody cages with resorbable PLLA (poly-L-lactide) cages. The latter had a potential advantage over the former, as their moduli of elasticity are closer to that of vertebral bone. As a result, with its gradual resorptive properties, bioresorbable implants gradually decrease the stress shielding, seen with rigid metallic implants. Also, flexible and less rigid bioabsorbable implants stabilize motion segments, while allowing a greater transfer of load to the host spine during resorption, potentially minimizing junctional degeneration.¹²⁶

In another approach, hydroxyapatite-collagen composites having a bone-like nanostructure was synthesized and shaped into implant. This study was to develop artificial vertebra using this novel implant for anterior fusion of the cervical spine. Histological and radiographical analysis after initial studies on beagle dogs suggested that the composite material adsorbing rhBMP (bone morphogenetic protein)-2 might be a suitable replacement for the existing ceramics in anterior inter body fusion of the cervical spine.¹²⁷

Summary

The full potential of bioceramics has only begun to be recognized presently, as an integral and vital segment of our modern health care delivery system. Based on a theoretical foundation, most of the developments to date are done by trial and error experiments. The maintenance of a pain-free life is made possible through devices designed and produced from bioceramic materials. The tailoring of composition, microstructure and molecular surface chemistry of various types of bioceramics to match the specific biological and metabolic requirement of tissues or disease states is being undertaken subsequently. The design of bioceramics on the basis of this molecular-based pharma-

ceutical approach may be coupled with tissue and genetic engineering, sensor technology and information processing for advanced applications. These materials have advantages over metals and polymers, as they have the same ionic constituents as bone, and exhibit excellent wear characteristics leading to absence of wear debris *in vivo*. Hence, there lies an endless future scope for the researchers and organizations working in the field of biomaterials to improve the performance and quality of these materials.

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