United Journal of Chemistry
An International open access

ISSN: 2581-7760
CODEN: UJC
www.unitedjchem.org
Volume 1; Issue; 2 December 2018; Page No. 172-183

Biomaterials and Their Medical Applications

Mohammed Yaqob Shareef*[1]

Ministry of Higher Education and Scientific Research,National University of Science & Technology, Thi Qar, Nasiriyah, Iraq.
Corresponding author Email: myshareef62@yahoo.com

Abstract:

Biocompatibility may therefore be defined as the ability of a material to induce/perform with an appropriate host response in a specific application[1,2]. The response should be such as to ensure the continued safe and effective performance of the material[1,2]. Furthermore, such materials should not be toxic or have unfavourable properties either due to direct contact or breakdown products. In addition, factors including physical, mechanical properties, design, and surface chemistry should also be considered carefully**.**

Keywords: Biomaterials, Biocompatibility, Physical and Mechanical Properties, Surface Chemistry, Materials/Tissue Interactions

INTRODUCTION

A biomaterial can be defined as any material, intended to interface with biological systems to treat, augment, or replace an organ or function of the body[1]. Any material used for this purpose, either in the oral cavity or another part of the body, therefore, has to be accepted by the bone and/or soft tissues. Biocompatibility may therefore be defined as the ability of a material to induce/perform with an appropriate host response in a specific application[1,2]. The response should be such as to ensure the continued safe and effective performance of the material [1,2]. Furthermore, such materials should not be toxic or have unfavourable properties either due to direct contact or breakdown products. In addition, factors including physical, mechanical properties, design, and surface chemistry should also be considered carefully.

There are a number of terms which are commonly used in the description of materials/tissue interactions and are therefore important in the study of the biocompatibility[1]:

1. Bone bonding has been defined as the establishment, by physico-chemical processes, of continuity between implant and bone matrix[1].
2. Osteoconductive materials can only guide bone formation on their surface when implanted in a bony environment.
3. Osteoinductive materials have the ability to induce bone formation when implanted in non-osseous tissues.
4. Osseointegration a direct structural and functional connection between ordered, living bone and the surface of a load carrying implant, as assessed at the light microscopical

(Received: December 01, 2018; Accepted: December 18, 2018)
Volume 1; Issue; 2 December 2018; Page No. 172-183
www.unitedjchem.org

level; modified from P-I Branemark, 1987[1-3].

5. Interdigitation is the intimate association of the collagen fibres of the extra-cellular bone matrix with a materials surface, especially finger like projections into the material[4].
6. Bioactive a biomaterial that is designed to elicit or modulate biological activity[1,2]. It can be defined also as the ability of a material to actively influence the surrounding tissue and the development of a response from the tissue. In the case of bone, to aid the formation of a bone/material bond. Chemical bonding of bone with bioactive materials gives them their 'direct' attachment and interfacial strength which prevents interfacial fracture[5].
7. Bioinert materials that do not interact with the tissues of the body; forming no direct attachment with body tissues[5].
8. Biodegradation the breakdown of a material mediated by a biological system[1].

A wide variety of different materials have been used for medical and dental applications[6,7]. For example, cobalt-chromium-molybdenum (Co-Cr-Mo) based alloys are used in the production of subperiosteal implants as they are easy to cast[6,8]. They are highly resistant to corrosion and are the hardest and least ductile of all metals used in the field of dentistry. One of the advantages of metal implants is the necessary sterilisation process that can be achieved with conventional methods. Pure titanium and Titanium-6 Aluminium-4 Vanadium (Ti6Al4V) are currently the most commonly used metallic implants. Experimentally it has been shown that titanium has the potential to osseointegrate[9].

Carbon is a material exhibiting varied and unique properties not found in any other material. By controlling the structure of carbon, pyrolytic carbon implants were manufactured as a second generation material. Several different types of carbons are very inert and have been investigated as both dental and orthopeadic implants. But possibly the most useful application of these materials is in the vascular system. Carbons have a very good compatibility with blood, and many forms of these materials have been developed. Due to their unusual structure, they do not suffer from fatigue failure which can be a problem with other implant materials[10,11]. However, clinical complications reported following carbon implants are osteomyelities, parasthesia, anaesthesia, and substantial bone loss[10-12]. As a consequence their use today is limited.

In general, polymers are softer and more flexible and not as strong as the other materials described above including ceramics. Hence they are not particularly suitable for dental implant systems that require high mechanical stiffness and strength. They are generally used as graft materials[2,6].

There are two major type of bioceramics, namely bioactive and bioinert ceramics[10]. The bioactive ceramics include hydroxyapatite (HAp), tricalcium phosphate (TCP), glass ionomer cement (GIC) and bioglass[13-17]. When these types of bioceramic are used as bone substitutes, the bone is directly chemically bonded to the material. However, these materials are mechanically weak and unsuitable for use in stress bearing areas. Alumina and zirconia are classified as bioinert ceramics which are tough and strong[13,15,16]. When such ceramics are implanted as a bone substitute they become surrounded by a fibrous tissue capsule which prevents direct bonding of the material to bone. Repeated stimulation by stress and tension at the interface leads to the growth of connective tissue, which increases the risk of loosening between the bone and ceramic implant.

Hydroxyapatite (HAp) ceramic has an excellent affinity to the bone because hydroxyapatite and other calcium phosphate are also the mineral components of bone[13-16]. HAp has inadequate strength and toughness to be used in stress bearing areas[17]. Two approaches have been taken to overcome this problem. Ducheyne et al.[17] used HAp as a surface layer on titanium implants, but this approach has several problems that include separation of the coating layer from the underlying bioinert matrix and the coating process can reduce the strength of the bioinert materials[13]. The second approach is to produce ceramic composites with better mechanical properties [17,18]. The hypothesis is that the even distribution of the apatite phase as islets in the strong matrix phase or visa versa will contribute to mineralization and direct bone apposition onto this type of ceramic composite[18-20].

Bone

The production and implantation of bone substitutes requires understanding of the nature of

bone. Bone can be defined as a mineralised form of connective tissue composed of collagen fibres dispersed in a matrix of bone mineral with other constituents such as blood vessels and bone cells dispersed throughout. Bone can thus be regarded as a composite tissue, composed of inorganic and organic material. The inorganic component is mainly calcium and phosphate in the form of hydroxyapatite, whereas the organic component is mainly collagen and a little water. Collagen forms about 86% by weight of the organic matrix of bone[21-23].

For all its rigidity, bone is by no means a permanent and immutable tissue. Throughout its hard extracellular matrix are channels and cavities occupied by living cells, which account for about 15% of the weight of compact bone. These cells are engaged in an unceasing process of remodeling: one class of cells removes old bone matrix while another deposits new bone matrix. These mechanisms provides for continuous turnover and replacement of the matrix in the interior of the bone.

There are three main cells in bone[21-25] namely:

1. osteoblasts, the bone-forming cells,
2. osteoclasts, the bone-resorbing cells and
3. osteocytes, which are of the connective-tissue cells family like fibroblasts and chondroblasts.

The bone matrix is secreted by osteoblasts that lie at the surface of the existing matrix into which it deposits fresh layers of bone. Some of the osteoblasts remain free at the surface, while others gradually become embedded in their own secretion. This freshly formed material (consisting chiefly of type I collagen) is called osteoid. It is rapidly converted into hard bone matrix by the deposition of calcium phosphate crystals. Once imprisoned in hard matrix, the original bone-forming cells, now called an osteocyte, has no opportunity to divide, although it continues to secrete further matrix in small quantities around itself. The osteocyte occupies a small cavity or lacuna in the matrix, but it is not isolated from other osteocytes. Tiny channels, or canaliculi, radiate from each lacuna and contain cell processes from the resident osteocyte, enabling it to form gap junctions with adjacent osteocytes[22,23]. Although the networks of osteocytes do not themselves secrete or erode substantial quantities of matrix, they probably play a part in controlling the activities of the cells.

While bone matrix is deposited by osteoblasts, it is eroded by osteoclasts. These large multinucleated cells originate, like macrophages, from hemopoietic stem cells in the bone marrow. The precursor cells are released as monocytes into the bloodstream and collect at sites of bone resorption, where they fuse to form the multinucleated osteoclasts, which cling to surfaces of the bone matrix and eat it away. Osteoclasts are capable of tunneling deep into the substance of compact bone, forming cavities that are then invaded by other cells. A blood capillary grows down the centre of such a tunnel, and the walls of the tunnel become lined with a layer of osteoblasts. To produce the plywood-like structure (known as haversian systems) of compact bone, these osteoblasts lay down concentric layers of new bone, which gradually fill the cavity, leaving only a narrow canal surrounding the new blood vessel.
Bone growth takes place in one of two possible ways it may grow directly in fibrous connective tissue (intramembraneous ossification) or it may grow from cartilage firstly (endochondral ossification). Most bones show evidence of both these processes. Both processes continue until the bone achieves its natural size, then the endochondral ossification stops. Intramembraneous growth continues throughout life and contributes to the remodelling process which makes bone a dynamic structure. Bone can grow only by appositional (surface) growth (that is, by the laying down of additional matrix and cells on the free surfaces of the hard tissue), whereas young cartilage is capable of interstitial growth.

Mechanical Properties of Bone

Bone is a very dense, hard, specialized form of connective tissue. Like reinforced concrete, bone matrix is predominantly a mixture of tough fibres (collagen fibrils), which resist pulling forces, and solid particles (calcium phosphate as hydroxyapatite crystals) which resist compression. The volume occupied by the collagen is nearly equal to that occupied by the calcium phosphate, which is designed to provide mechanical support for skeletal motion and protect nonmineralized structures [22-24,26]. Its properties are a consequence of mineralized collagenous tissue structures that are continually remodelled in response to applied stess. Therefore, the mechanical properties of bone are dependent on the type of loading and the mineral content.

Collagen fibres in osteon units are unable to withstand compressive forces in the absence of hydroxyapatite that is deposited within the hole region and between fibres. The mineral composition of bony tissue varies from 30-90% for compact (cortical) bone and 5-50% for spongy (cancellous) bone. The elastic modulus is dependent on the porosity and increases with calcium content. The mechanical properties of bone were reviewed by Wasserman and Dunn[26] and some pertinent data are presented in the following table:

Cancellous bone, also called trabecular or spongy bone, is less dense than cortical bone and consequently has a lower modulus of elasticity and higher strain to failure, 5 to 7%. The difference in stiffness between the two types of natural bone tissues ensures a gradient in mechanical load across a bone.

Many types of implants for repair of the skeletal system are in contact with both trabecular and cortical bone. It is impossible for most prosthesis materials to produce similar gradients of stiffness between an implant and its host tissue.

The problem with a mismatch in elastic modulus across an interface is that the higher modulus implant (a limitation of bioinert ceramics is that materials with high fracture toughness and high flexural strength also tend to have a high elastic modulus and a low bioactive index) will carry most of the load. The bone will be ''stress shielded''. which is undesirable because living bone must be under some tensile load to remain healthy. Bone that is unloaded or loaded in compression will undergo a biological change that leads to resorption and weakening. The interface between stress shielded bone and an implant will deteriorate as the bone structure is weakened.

Table 1: Mechanical properties of long bone and skull

Site	Modulus of Elasticity (GPa)	Strength (MPa)	
		Tensile	Compressive
Long bone	18	136	150
Skull	5.6	48	96

All bioactive materials form a mechanically strong interfacial bond with bone, but most bioactive ceramics have a flexural strength and fracture toughness that is less than bone. Because of these biomechanical limitations, clinical use of bioactive ceramics has been restricted.

Healing of Bone

Following fracture of bone or implantation of material the trauma initially disrupts the normal blood circulation of the local bone and the adjoining soft tissue[21,22]. The local feeding vessels, which are the central capillaries passing through the haversian systems, are damaged. Blood from the damaged vessels flows out to surround the implanted material and fill any cavities in the bone and soft tissue. Osteocytes cut off from the nutrient supply die and the bone undergoes necrosis as far as the nearest unaffected canal. The degradation of tissue gives rise to free radicals which exert a weak bacteriocidal effect and stimulate fibroblasts to proliferate and attract macrophages. Osteoclasts invade the dead bone and resorb necrotic cells and bone matrix. Complimentary to this, osteogenic cells proliferate to begin the reconstruction of bone by elaboration of a non-mineralised collagenous matrix (osteoid), which subsequently undergoes calcification [22,23]. A material placed to act as a bone substitute should be designed to aid the above process and materials that exert a toxic effect on the cellular processes of healing/repair should be excluded from consideration.

Bioceramics

The potential of ceramics as biomaterials relies upon their compatibility with the physiological environment. Bioceramics are defined as ceramic biomaterials designed to achieve a specific physiological response when used as a material of construction for prosthetic devices or artificial internal organs. The compatibility of bioceramics is the result of the fact that they can be composed of ions commonly found in the physiological environment, these are Calcium, Potassium, Magnesium, Sodium, and of ions showing limited toxicity to body tissue such as Aluminium and Titanium[27-29].

Ceramics fulfil many of the criteria of prosthetic materials. They are corrosion resistant, strong and have a high degree of biocompatibility.

As a result, over the last decade ceramics have been increasingly studied with a view to their use as permanent implantable materials.

The first ceramics to be used as prosthetic materials were mainly alumina, titania and mixtures of calcia and alumina. These materials differ chemically from the composition of calcium phosphate ceramics, which may be why these materials did not integrate with the bone tissue[28,29].

Bioceramics are classified into three sub-groups, based upon their chemical reactivity in a physiological environment:

1. Bioinert such as ZrO_2 and Al_2O_3,
2. Bioactive such as HAp and Bioglasses and
3. Resorbable such as tricalcium phosphate, TCP,[27,28].

Bioinert Materials

Inert bioceramics or non-toxic inactive bioceramics undergo little or no chemical change during long-term exposure to the physiological environment. Even in those cases where the bioceramics may undergo some long-term chemical or mechanical degradation, the concentration of the degradation products in the adjacent tissue is easily controlled by the body's natural regulatory mechanism[29].

Bone response to bioinert ceramics involves the formation of a very thin of fibrous membrane, several micrometers or less, surrounding the implant material. Bioinert ceramics are attached to the physiological system through mechanical interlocking, resulting from tissue ingrowth into undulating surfaces.

Alumina

One of the most widely employed bioinert ceramics is alumina (Al_2O_3). The first use of aluminas for implants in orthopaedics and dentistry was in the 1960s[30,31] and they were employed in hip prostheses as early as 1970[31]. Since those early days the quality and performance of aluminas have improved[31-33] and high-purity, fine-grained aluminas are currently used for a wide range of medical applications, e.g. dental implants, middle ear implants, and hip and knee prostheses[31,32].

Although the aluminas currently available perform satisfactorily, a further improvement in strength and toughness would increase mechanical safety and may extent usage to higher stressed components. There are many reports comparing implant made of alumina ceramics to those made of stainless steel, on the basis of their resistance to corrosion or cytotoxity[27-29,34,35]. It is generally believed that alumina ceramics are superior to stainless steel in terms of the affinity of bone to these biomaterials in vivo[36-40]. However, alumina is sensitive to microstructural flaws which leads to a poor resistance to stress concentrations or mechanical impact in service[39,41].

Zirconia

Zirconia (ZrO_2) is also classified as a bioinert ceramic[42] and is noteworthy for its high strength and toughness. Zirconia has three crystal phases: monoclinic, tetragonal, and cubic. Cubic-phase of zirconia is stable but brittle. Stress-induced transformation of the tetragonal phase to the monoclinic phase has been shown to increase the fracture toughness[42-45]. Through this phase transformation, zirconia has been shown to have a high fracture toughness. Phase transformation from tetragonal to monoclinic crystals, on the other hand, might result in a loss of strength with time[46].

In addition, zirconia has demonstrated better wear resistance than alumina and metal alloys in some experiments and is thus considered to be a desirable and promising joint material[45]. However, there is controversy about possible time-dependent deterioration in its mechanical properties,[47,48] which make orthopaedic surgeons hesitant about using zirconia[49]. Nevertheless zirconia, has become a material of great interest for medical and dental implant use as shown in biologic and histopathologic studies[50,51]. Partially stabilised zirconia has been shown to be tissue compatible,[51,52] and to possess twice the bending strength of polycrystalline alumina[52].

Bioactive Materials

In bioactive or non-toxic active bioceramics, the composition is designed such that the surface undergoes a selective chemical reaction with the physiological environment, resulting in a chemical bond between tissue and the implant surface[27-29].

The bonded interface protects the implant material from further deterioration with time. The main application of bioactive ceramics are in the area of ossicular bone replacement prostheses, as coating for orthopaedic applications and as dental implant materials.

Non-toxic resorbable bioceramics compositions contain only elements that are easily processed through normal metabolic pathways, such as calcium and phosphorous. The function of non-toxic, totally resorbable bioceramics is to serve as a scaffold or filler of space permitting tissue infiltration and replacement. The main applications of non-toxic resorbable bioceramics is in the area of treatment of maxillofacial defects and for the oblitration of periodontal pockets.

Bioglass

The first man-made materials which were found to bond to living bone were glasses in system Na_2O-CaO-SiO_2-P_2O_5. These were discovered by Hench et al.[53] in the early 1970s and named Bioglasses, which can be classified as a bioactive material[54]. The bioglass material seems to enhance bone-implant interface development and bonding when implanted in bone[54-56]. A number of interfacial bonding mechanisms for bioactive glass substrata have been hypothesised by Hench et al.[53] and others[54-57]. These included mechanical interlocking and physical or chemical interactions, while similar mechanisms have been described for calcium ceramics by Jarcho et al.[58] when bioglasses are subjected to an aqueous environment, calcium and phosphate ions leach from the implant bulk to form a calcium phosphate-rich layer on the implant surface, that is believed to impart the bone bonding ability to the bioglasses. Biological processes, such as collagen interdigitation, have been described by Hench et al.[54,55,59-61] and possibly underlie bone bonding with surface reactive glasses.

Since the discovery of bioglass in early 1970s, various kinds of glasses and glass-ceramics have also been found to bond to living bone, and those are already clinically used such as an artificial middle ear bone[59] and alveolar ridge maintenance implants[62,63]. Bioglass is also used as artificial vertebrae, intervertebral spacers, iliac crest prostheses, and granules for bone defect fillers[61-63].

Glass Ionomer Cement

Glass ionomer cement (GIC) was orginally developed by Wilson and Kent in 1969 and is widely used as a dental restorative material. Biological evaluation has concentrated on the in vitro[64,65] and in vivo[66-68] responses of the dental pulp to GIC and compares favourably with other types of dental filling materials[64,69]. Brook[21] in his in vivo and in vitro study has confirmed that GICs showed a favourable biological response as potential bone substitutes, when compared to HAp and TCP ceramics. Brook reported also that GICs are a class of materials suitable for use as bone substitutes and cements and that GICs are bioactive materials releasing F-, Ca2+, PO42-, and SiO42-. Fluoride in a low systemic dose has been shown to stimulate bone formation[22,70]. The release of calcium ions may increase the degree of supersaturation of this ion in the tissue fluid adjacent to the implant and the silicate ion might provide favourable sites for the nucleation of apatite on the surface of the GIC which has been postulated to explain the bioactive response of bioactive bioglasses to bone[71].

Calcium Phosphates

The fact that the mineral phase of bones and teeth is composed of calcium phosphate salts, has directed researchers to investigate these materials as potential candidates for bone substitutes. Although the mineral is similar to hydroxyapatite (HAp), it is poorly crystalline in structure and contains a wide range of calcium phosphate phases, including TCP, carbonated apatite and numerous other ionic impurities such as fluoride, magnesium and sodium[72-74]. The development of synthetic calcium phosphates has provided a wide range of materials to be investigated for their bone replacement properties and may be the most biocompatible artificial bone substitutes currently used in the clinic. The common clinical applications of calcium phosphate ceramics are for jaw augmentation[74,75] and tooth root replacement[76], although their application is limited due to its poor biomechanical performance. These materials can bond with natural bone without fibrous tissue encapsulation[77-81]. The favourable response of the calcium phosphate ceramics, despite variations in the chemical composition and material structure, is attributable to their being mainly composed of calcium and phosphate ions[81,82].

Hydroxyapatite (HAp)

HAp with the chemical composition Ca10(PO4)6(OH)2 has been extensively study as a bone substitute. It shows good biocompatibility when implanted in either soft tissue[83-85], or hard tissue[82,86-88] and can form strong and intimate bond with bone[85-87]. Driskell et al.[89] was the first to report that a chemical bond exists between bone and HAp. HAp, when sintered at high temperatures of up to 1250 oC, was initially believed to be non-resorbable[83]. However, it is currently generally accepted that degradation of HAp can occur to a certain extent[82,90]. LeGeros, et al.[91] reported that the bioactivity of HAp may be related to its dissolution rate.

Fluorapatite (FA)

Fluorapatite Ca10(PO4)6(F)2 exhibits the same structure as HAp, the only difference being that the hydroxyl groups have been replaced by fluorine ions. The satisfactory biocompatibility of FA have been described by various investigators[92-94], while Lugscheider et al.[95] reported that FA is more stable than HAp at high temperatures, and more resistant to acid attack. It would therefore be more suitable than HAp for high temperature processes such as plasma spraying, which was confirmed by Dhert[94,96].

Tricalcium Phosphate (whitlockite)

Tricalcium phosphate Ca3(PO4)2 (TCP), together with HAp, is one of the most widely investigated calcium phosphate ceramics. TCP can be found in two forms, *-TCP and the more stable *-TCP. Both forms have been reported to exhibit relatively high dissolution properties[97-99]. TCP has been reported to possess good biocompatible properties[97,98,100,101]. Klein et al.[100] reported less bone contact and bone remodelling around plasma sprayed *-TCP implants in dog femora, as opposed to plasma sprayed HAp and tetracalcium phosphate implants. Furthermore, it is thought to be less suitable as a plasma sprayed layer, due to its degradation character[94], and therefore is currently used primarly as a bone filler.

Tetracalcium Phosphate

Very little information is available for Ca4(PO4)2O (TTCP) as a bone substitute material. Similar interface morphologies as that with HAp were observed when TTCP was implanted in bone tissue[100,102]. Yoshimine, et al.[103] in their ultrastructural examination, showed that osteogenesis occurred directly on the surface of TTCP. This suggest that TTCP is biocompatible and possesses osteoconductive properties.

Future Direction and Applications

1. Nanostrutured ceramics will be produced that demonstrate even higher degree of integration between biomaterials and the biological environment[104].
2. To date, a large part of the interest has continued on titanium oxide (TiO2) nanotube because it is well known that titanium (Ti) is a biocompatible orthopaedic material which provides an excellent osseointegrative surface. Yet, little notice has been given to zirconium dioxide (ZrO2) nanotube[105].
3. The mechanical properties have been found to be superior to those of the generally used Ti-6Al-4V alloy[106].
4. There is a huge parametric space in which to explore novel nanostructures, nanopore dimensions and material compositions for improving and developing implant designs for anticipated tissue interactions.

REFERENCES

1. Williams D. F., Black, J. and Doherty P. J. Second Consensus Conference on Definitions in Biomaterials, In: Biomaterial-tissue interfaces; Advances in Biomaterials vol., Doherty et al. (eds), Elsevier Science Publishers, London, 10: 525-533, 1992.
2. Williams, D. F. Review Biodegradation of Surgical Polymers. J. Mat. Sci. 17: 1233-1246, 1982.
3. Branemark P. I., Osseointegration and its Experimental Background. J. Prosthet. Dent. 50: 399-412, 1983.
4. Davis, J. E. and Matsuda, T. Extracellular matrix production by osteoblasts on bioactive substrata in vitro. Scanning Microscopy 2(3): 1445-1452, 1988.
5. Le Geros, R. Z., Orly, I. Gegoire, M. and Deculsi, G. Substrate surface dissolution

and interfacial biological mineralisation. In: the bone biomaterial interface. Davies, J. E. (ed.). Univ. Toronto Press, 76-88, 1991.

6. Lemons, J.E., Natiella, J. Biomaterials, biocompatibility and pre-implant considerations. Dent. Clin. N. Am. 30: 3-23, 1986.
7. Jarcho, M. Biomaterial aspects of calcium phosphates properties and applications, Dent. Clin. N. Am. 30: 25-47, 1986.
8. Meffert, R. M., Langer, B. and Fritz, M. E., Dental implants: a review. J. Periodontol. 63: 859-870, 1992.
9. Young, F. A. Future directions in dental implants research. J. Dent. Educ. 52: 770-774, 1988.
10. Kent, J.N. and Bokros, J.C. Pyrolytic carbon and carbon-caoted metallic dental implants. Dent. Clin. N. Am. 24: 465-504, 1980.
11. Schnitman, P.A. and Shulman, L. B. Vitreous carbon implants. Dent. Clin. N. Am. 3: 441-463, 1980.
12. Mah, C. The evaluation of implants over the last fifty years. Aust. Prosthodont. J. 4: 47-52, 1990.
13. Suda, A., Sato, T., Takagi, M., Osanai, T. and Suzuki O. Biocompatibility of zirconia dispersed hydroxyapatite ceramics, J. Jpn. Orthop. Assoc. 64: 249-259, 1990.
14. Hench, L. L. and Paschall, H. A. Direct bond of bioactive glass-ceramic materials to bone and muscle, J. Biomed. Mater. Res. 4: 25-43, 1973.
15. Hench, L. L. and Paschall, H. A. Histochemical responses at a biomaterial's interface, J. Biomed. Mater. Res. Symp. 5: 49-64, 1974.
16. Gross, U. M., Brandes, J., Strunz, V., Bab, I. and Sela, J. The ultrastructure of the interface between a glass ceramic and bone, J. Biomed. Mater. Res. 15: 291-305, 1981.
17. Ducheyne, P., Hench, L.L., Kagan, A., Martens, M., Burssens, A., and Mulier, J.C. Effect of hydroxyapatite impregnation on skeletal bonding of porous coated implants, J. Biomed. Mater. Res. 14: 225-337, 1980.
18. Wu, J-M. and Jeh, T-S. Sintering of hydroxyapatite-zirconia composite materials., J. Mater. Sci: Mater. Med. 23: 3771- 3777, 1988.
19. Li, J., Hermansson, L. and Soremark, R. High-strength biofunctional zirconia: mechanical properties and static fatigue behaviour of zirconia-apatite composites, J Mater. Sci: Mater. Med. 4: 50-54, 1993.
20. Takagi, M., Mochida, M., Uchida, N., Saito, K. and Uematsu, K. Filter cake forming and hot isostatic pressing for TZP-dispersed hydroxyapatite composite, J. Mater. Sci.: Mater. Med. 3: 199-203, 1992.
21. Brook, I. Evaluation of glass-ionomer cements for use as bone substitutes with reference to their value for treatment of atrophic alveolar bone, Ph.D Thesis University of Sheffield, UK, 1993.
22. Prichard J.J. General anatomy and histology of bone. In: Biochemistry and physiology of bone Bourne,G.M. (ed). Academic Press, New York, 1965.
23. Ravaglioli A. and Krajewski, Physical properties and physiology of bone. Pub Chapman and Hall, London, 16-39, 1992.
24. Herman, S. Cheug and Michael, H. Growth of osteoblasts on porous calcium phosphate ceramics: an in vivo model for biocompatibility study. J. Biomaterials. 10: 63-67, 1989.
25. Davies J.E. The use of cells and tissue culture to investigate bone cell reactions to bioactive materials, In: Handbook of bioactive Ceramics. Vol. I, Yamamuro T et al. eds. CRC Press, Boca Raton, Fl, USA, 1: 1-65, 1990.
26. Wasserman, A. J. and Dunn, M. G. Morphology and mechanics of skin, cartilage and bone. In applications of Biomaterials in facial plastic Surgery (Eds Glasgold and Silver, F. H.), CRC Press, Boca Raton Fl., 1991.
27. Heimke, G. Bioinert Ceramics in Surgery, In: Ceramics in Surgery, Vincenzini P. (Ed), Elsevier, Amsterdam, The Netherlands, 17: 33-47, 1983.
28. Hulber, S.F., Hench, L.L., Forbes, D. and Bowman, L. S. History of bioceramics, In: Ceramics in Surgery (Ed. P. Vincenzini), Elsevier, Amsterdam, The Netherlands, 17: 3-29, 1983.
29. Kotoura, Y., Yamamuro, T., Shikata, J., Kakutani, Y., Kitsugi, T. and Tanaka, H., A. Method for toxicological evaluation of biomaterials based on colony formation of cells, Arch. Orthop. Trauma Surg. 104: 15-19, 1985.

30. Smith, L. Ceramic-plastic materials for bone substitutes, Arch. Surg. 87: 653-661, 1963.
31. Sandhaus, S. Bone implants and drills and taps for bone surgery, British Patent 108: 37-69, 1967.
32. Dalgleish, B.J. and Rawlings, R.D. A comparison of the mechanical behaviour of aluminas in air and simulated body environments, J. Biomed. Mater. Res. 15: 527-542, 1981.
33. Implants for Surgery-ceramic materials based on alumina, International Standard, ISO 6474, 1981.
34. Ioku, K., Yoshimura, M. and Somiya, S. Microstructure and mechanical properties of hydroxyapatite ceramics with zirconia dispersion prepared by post-sintering, Biomaterials, 11: 57-61, 1990.
35. Semlitsch, M., Lehmann, M., Weber, H., Dorre, E. and Willert, H. G. New prospect for a prolonged functional life-span of artificial hip joints by using the material combination polyethylene/alumina oxide ceramic/metal, J. Biomed. Mater. Res., 11: 537-552, 1977.
36. Williams, D.F. Corrosion of orthopaedic implants (Ed. D.F. Williams), CRC Press, Boca Raton, FL, USA, 1: 197-229, 1982.
37. Griss, P., von Andrian-Werburg, H., Krempien, B. and Heimke, G. Biological activity and histocompatibility of dense Al2O3/MgO ceramic implant in rats, J Biomed. Mater. Res., 4: 453-462, 1973.
38. Griss, P., Krempien, B., von Andrian-Werburg, H., Krempien, B., Heimke, G., Fleiner, R. and Diehm, H. Experimental analysis of ceramic-tissue interactions. A morphologic, and radiographic study on dense alumina oxide ceramic in various animals, J. Biomed. Mater. Res. 5: 39-48, 1974.
39. Hentrich, R.L., Graves, G.A., Stein, H.G. and Bajpai, P.K. An evaluation of inert and resorbable ceramics for future clinical orthopeadic applications, J. Biomed. Res., 5: 25-51, 1971.
40. Hayashi, K., Matsuguchi, N., Uenoyama, K. and Sugioka, Y. Re-evaluation of the biocompatibility of bioinert ceramics in vivo, Biomaterials, 13(4):195-200, 1992.
41. Hulbert, S.F., Young, F.A., Mathews, R.S., Klawitter, J.J., Talbert, C.D. and Stelling, F. H. Potential of ceramic materials as permanently implantable skeletal prostheses, J. Biomed. Mater. Res. 4: 433-456, 1970.
42. Akagawa, Y. Hashimoto, M. Kondo, N. Satomi, K. Takata, T. Tsuru, H. Initial bone-implant interfaces of submergible and supramergible endosseous implants. J. Prosthet. Dent. 55: 96-100. 1986.
43. Matsuhashi, T. Ichihara, M. and Tatsuke, U. Characterization and stabilization of metastable tetragonal zirconia, J. Am. Ceram. Soc. 57: 97-101, 1974.
44. Porter, D. L. and Heuer, H. Reply to further discussion of precipitation in partially stabilized zirconia, J. Am. Ceram. Soc., 60: 280-281, 1977.
45. Shimizu, K. Oka, M. Kumar, P. Kotoura, Y. Yamamuro, T. Makinouchi, K. and Nakamura, T. Time-dependent changes in the mechanical properties of zirconia ceramic. J. Biomed. Mater. Res. 27: 729-734. 1993.
46. Pascoe, R.T., Hughan, R.R. and Garvie, R.C. Strong and tough zirconia ceramics, Sci. Sinter. 11: 185-192, 1979.
47. Sato, T. and Simada, M. Transformation of yttria-doped tetragonal zirconia polycrystals (Y-TZP) by annealing in water. J. Am. Ceram. Soc. 68: 356-360, 1985.
48. Torre, J. P. Manufacture and engineering properties of ceramics, In: Proceeding of the Material Engineering Conference, U. K. Mechanical Engineering Publications Ltd. London, 5-9, Novmber, 1986.
49. Christel, P. Meunier, A. and Heller, M. Mechanical properties and short-term in vivo evaluation of yttrium oxide-partially stabilized zirconia. J. Biomed. Mater. Res. 23: 4561, 1989.
50. Minamizato T. Slip-cast zirconia dental roots with tunnels drilled by laser process. J. Prosthet. Dent. 63: 677-684. 1990.
51. Nagai, N. Takeshita, N. Hayashi, J. Biological reaction of zirconia ceramic as a new implant material in the dental field. Jpn. J. Oral Biol. 24:759-762. 1982.
52. Ichikawa, Y., Akagawa, Y., Nikai, H., and Tsuru, H. Tissue compatibility and stability of a new zirconia ceramic in vivo., J. Prosthetic Dent. 68: 322-326. 1992.
53. Hench, L.L., Splinter, R. J., Allen, W.C. and

Greenlee, T.K. Bonding mechanisms at the interface of ceramic prosthetic materials. J. Biomed. Mater. Res. Symp. 2(2): 117-141, 1972.

54. Gross U.M. Biocompatibility- The interaction of biomaterials and the host response. J. Dent. Ed. 52: 798-803, 1988.
55. Hench, L.L. Surface reaction kinetics and adsorption of biological moieties: A mechanistic approach to tissue attachment, In: The Bone-Biomaterial Interface, Davies, JE (ed.), University of Toronto Press, Toronto, 33-48, 1991.
56. van Blitterswijk, C.A., Leenders, H. and Bakker, D. Interfacial reactions leading to bone-bonding with PEO/PBT copolymers (polyactive), In: Bone-Bonding Biomaterials, Duchyene, P, Kokubo, T. and van Blitterswijk, C.A. (eds), Reed Health Care Communications, Leiderdorp, 13-30, 1992.
57. Matsuda T., Inoue, N. and Kamegai, T. A histological comparison of the tissue interface of bioglass and silica glass. J. Biomed. Mater. Res. 21: 485-497, 1987.
58. Jarcho, M. Calcium phosphate ceramics as hard tissue prosthetics, Clin. Orthop. Res., 157: 259-278, 1981.
59. Hench, L.L., and Wilson, J. Surface-active biomaterials. Science, 226: 630-636, 1984.
60. Hench, L.L. and Ethridge, E.C. Biomaterials, an interfacial Approach. Academic Press, New York, 137, 1982.
61. Hench, L.L., Biomaterials: From Concept to Clinic. J. Am. Ceram. Soc. 74: 1487-1510, 1991.
62. Vogel, W. and Holland, W. The Development of Bioglass Ceramics for Medical Applications. Angew. Chem. Int. U.K. (Ed) 26: 527-544, 1987.
63. Wilson, J. Clinical Application of Bioglass In Glass: Current issues. A.F. Wright and J. Dupuy. (Eds) Martinus Nijhoff Pub. Dordrecht. 662-669, 1985.
64. Kawahara H., Imanishi Y. and Oshima H. Biological evaluation on glass ionomer cement. J. Dent. Res. 58(3): 1080-1086, 1979.
65. Hetem S., Jowett A.K. and Ferguson M.W.J. Biocompatibility testing of a posterior composite and dental cements using a new organ culture model. J. Dent. Res., 17: 155-161, 1989.
66. Plant C.G., Tobias R.S., Britton A.S., and Rippin J.W. Pulpal response to a glass-ionomer luting cement. Brit. Dent. J., 165: 54-58, 1988.
67. Pameijer C.H. and Stanley, H.R. Biocompatibility of a glass ionomer luting agent in primates. Part I. Am. J. Dent., 1(2): 71-75, 1988.
68. Zetterqvist L., Anneroth G. and Nordenram A. Glass-ionomer cement as retrograde filling material. An experimental investigation in monkeys. Int. J. Oral. Maxillofac. Surg., 16: 459-464, 1987.
69. Jonck L.M., Grobbelaar C.J. and Strating H. Biological evaluation of glass-ionomer cement. (ketac-0) as an interface material in total joint replacement. A screening test. Clin. Materials., 4: 201-224, 1989.
70. Tirner R. T., Francis R., Brown D., Gerand J., Hannon K.S. and Bell N.H. The effects of fluoride on bone and implant histomorphometry in growing rats. J. Bone Miner. Res., 4(4): 477-484, 1989.
71. Kokubo K., Kushitani H., Ontsuki C., Sakka. and Yamamuro T. The effects of ions dissolved from bioactive glass ceramic on surface apatite formation. J. Mater. Sci. Med., 4: 1-4, 1993.
72. de Groot, K. Ceramics of calcium phosphates: Preparation and properties In: Bioceramics of calcium Phosphates, de Groot (ed), CRC Press, Boca Raton, FI, USA, 100-114, 1983.
73. Driessens F.C.M. Formation and stability of calcium phosphates in relation to the phase composition of the mineral in calcified tissues, In Bioceramics of calcium Phosphates, de Groot (ed), CRC Press, Boca Raton, FI, USA, 1-32, 1983.
74. Nancollas G.H. and Zawacki, S.J. Calcium phosphate mineralization, Conn. Tissue Res. 21: 239-246, 1989.
75. Brook I.M., Graig G. T., et al. Management of the mobile fibrous ridge in atrophic maxilla using porous hydroxyapatite blocks. Brit. Dent. J. 162: 413-420,1987.
76. Brook I.M. and Lamb D.J. The use of particulate and block forms of hydroxyapatite

for local augmentation. Int. J. Oral and Maxillofac. Implants 2: 85-89, 1987.

77. de Putter C., de Lange G.I. and de Groot K. Permucosal dental implants of dense hydroxyapatite, evaluation and prognosis of their retention in alveolar bone. In Biological and biomechanical preformance of biomaterials. Ed. P. Christel et al. Elsevier Sci. Amsterdam., 111-116, 1986.
78. Frame J.W., Rout P.G.J. and Browne R.M. Ridge augmentation using solid and porous hydroxyapatite particles with and without autogenous bone or plaster. J.Oral Maxillofac. Surg., 45: 771-775, 1987.
79. White E. and Shors E.C. Biomatertial aspects of Interpore-200 porous hydroxyapatite. Dent. Clin. N. Am. 30: 49-67, 1987.
80. Davies J.E. and Matsuda T. Extracellular matrix production by osteoblasts on bioactive substrata in vitro. Scanning Microscopy, 2(3): 1445-1452, 1988.
81. Jarcho M., Kay J.F. and Gumaer K.I. Tissue cellular and subcellular events at a bone ceramic hydroxyapatite interface. J. BioEng. 1: 79-92, 1977.
82. van Blitterswijk., Grote J.J., Kwijpers C.J.G., van Hock B. and Daems W.T.H. Bioreactions at the tissue hydroxyapatite interface. Biomaterials, 6: 241-251, 1985.
83. Ogiso, M., Kaneda, H. Arasaki, J and Tabata, T. Epithelial attachment and bone tissue formation on the surface of hydroxyapatite ceramics dental implants, In: Biomaterials 1980, Winter GD et al. (eds), John Wiley and Sons Ltd, London, pp 59-64, 1982.
84. Jansen, J.A., de Wijn J.R., Wolters-Lutgerhorst, J.M.L. and van Mullem P.J. Ultrastructural study of epithelial cells attachment to implant materials. J. Dent. Res. 64: 891-896, 1985.
85. van Blitterswijk, C.A., Hesseling, S.C., Grote, J.J., Koerten, H.K. and de Groot, K. The biocompatibility of hydroxyapatite ceramic: Astudy of retrieved human middle ear implants. J. Biomed. Mater. Res. 24: 433-453, 1990.
86. Jarcho, M. Kay, J.F. Kennenth, I. Gumaer, K.I. Doremus, R.H. and Drobeck, H.P. Tissue cellular and subcellular events at a bone-ceramic hydroxyapatite interface, J. Bioeng. 1: 79-92, 1977.
87. Denissen, H. W., de Groot, K., Makkes, PCh, van den Hoff, A. and Klopper, P.J. Tissue response to dense apatite implants in rats. J. Biomed. Mater. Res. 14: 713-721, 1980.
88. de Groot, K. Degradable ceramics, In: Biocompatibility of implant materials, Williams, DF (ed), CRC Press, Boca Raton, Fl, USA, 1: 199, 1981.
89. Driskell, T.D., Hassler, C.R., Tennery, V.J., McCoy, I.R. and Clarke, W.J. Calcium phosphate resorbable ceramic: a potential alternative for bone grafting. J. Dent. Res. 52: 123-131, 1973.
90. van Blitterswijk, C.A. and Grote, J.J. Biological performance of ceramics during inflammation and infection, In: CRC Critical Reviews in Biocompatibility, 5: 13-43, 1989.
91. LeGeros, R. Z., Daculsi, G. Orly, I. Gregoire, M. Heughebaert, M. Gineste, M. and Kijkowska, Formation of carbonate apatite on calcium phosphate materials: Dissolution/ precipitation processes, In: Bone-bonding biomaterials, Ducheyne P. et al. (Eds), Reed Healthcare Communications, Leiderdorp, The Netherlands, 201-112, 1992.
92. Davis, SD, Gibbons, DF, Martin, RL, Levitt, S.R., Smith, J. and Harrington, R.V., Biocompatibility of ceramic implants in soft tissue, J. Biomed. Mater. Res. 6: 425-449, 1972.
93. Heling, I., Heindel, R. and Merin, B. Calcium-flouroapatite. A new material for bone implants, J. oral. Implant., 9: 548-555, 1981.
94. Dhert, W.J.A., Plasma-sprayed coatings and hard tissue compatibility. A comparative study on fluorapatite, magnesium whitelockite and hydroxyapatite, Ph.D. Thesis, Leiden University, The Netherlands, 1993.
95. Lugsheider, E. Weber, T. and Knepper, M. Production of biocompatible coatings of hydroxyapatite and fluorapatite, In: Proc. Natl. Thermal Spray Conference, Cincinatti, USA, 1988.
96. Driessens, F.C.M., Relation between apatite solubility and anti-carcinogenic effect of fluoride, Nature, 243: 420-421, 1973.
97. Kein, C.P.A.T., Calcium phosphate implant materials and biodegradation, Ph.D. Thesis, Free University, Amsterdam, The Netherlands, 1983.

98. Klein, C.P.A.T., Driessen, A.A., de Groot, K. and van den Hooff, A. Biodegradation behaviour of various calcium phosphate materials in bone tissue, J. Biomed. Mater. Res. 17: 769-782, 1983.
99. Klein, C.P.A.T., de Blieck-Hogervorst, J.M.A., Wolke, JGC and de Groot, K. Solubility of hydroxyapatite, tricalcium phosphate and tetracalcium phosphate coatings in vitro. Adv. Biomaterials. 9: 277-282, 1990.
100. Klein C.P. A.T., Patka P., van der Lubbe H.B.M., Wolke J.G. C., de Groot K. Plasma-sprayed coatings of tetracalcium, hydroxyapatite and TCP on titanium alloy: an interface study. J Biomed. Mater. Res. 25: 53, 1991.
101. van Blitterswijk, C.A., Grote, J.J., Koerten, H.K. and Kuijpers, W. Biological performance of B-whitlockite. A study in the non-infected and infected rat middle ear. J. Biomed. Mater. Res. 20: 1197-1217, 1986.
102. van Blitterswijk, C.A., de Wijn, J.R. Leenders, H, van den Brink, J. Hesseling, S.C. and Bakker, D. A comparetive study of interactions of two calcium phosphates, PEO/PBT copolymer and silicone rubber with bone and fibrous tissue, Cells and Materials, 3: 11-22, 1993.
103. Yoshimine, Y., Akamine, A., Mukai, M., Maeda, K., Matsukura, M., Kimura, Y. and Makishima, T. Biocompatibility of tetracalcium phosphate cement when used as a bone substitute., Biomaterials, 14(6): 403-406, 1993.
104. Narayan, Roger, Prashant Kumta, Charles Sfeir, Dong-Hyun Lee, Daiwon Choi, and Dana Olton, Nanostructured Ceramics in Medical Devices: Applications and Prospects. JOM Journal of the Minerals, Metals and Materials Society 56(10): 38-43, 2004.
105. Oliveira, N.T., Biaggio, S.R., Rocha-Filho, R.C., and Bocchi, N. Electrochemical Studies on Zirconium and Its Biocompatible Alloys Ti-50zr At.% and Zr-2.5nb Wt.% in Simulated Physiologic Media. Journal of Biomedical Materials Research Part A 74(3): 397-407, 2005.
106. Kobayashi, E., S. Matsumoto, H. Doi, T. Yoneyama, and Hamanaka, H. Mechanical Properties of the Binary Titanium-Zirconium Alloys and Their Potential for Biomedical Materials. J Biomed Mater Res 29(8): 943-50, 1995.