Advanced Ceramics for Biomedical Applications

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Bioinert Ceramics
Bioactive Ceramics
Glass and Oxide Ceramics
Implant Devices

1. Introduction

The broad exploration of the possible improvement of hard tissue replacements by the application of ceramic materials was initiated by *Hulbert*[1] and *Hench*[2] in the late 1960's. It was soon realized that, from the large number of ceramic materials, only a few have a combination of properties which made them reasonable candidates for uses in reconstructive surgery. These few have been grouped into two main categories according to the reactions they provoke in the surrounding bony tissue: The one does not or nearly not influence the adjacent tissue biochemically. Therefore, it was termed "bioinert". The materials in the other group were found to have a really fascinating ability; they can bond to living bony tissue in the sense of a gluing effect, but without the addition of an adhesive. They are called "bioactive" materials.

From the point of view of the introduction of these ceramics into medicine it might be called a happy coincidence that, at about the time these materials became available to implantology, some inadequacies of the previously used materials and material combinations were realized: In the mid 1960's, total hip replacements had become a standard treatment after the introduction of polymethylmethacrylate (PMMA) as the so-called bone cement.[3] By 1970, increased reoperations stimulated efforts to find the causes for the failures. In the early 1970's, it was widely agreed that the soft tissue layer, which separates the surface of the PMMA along most parts of the interface from the normally proliferating bony tissue, is the weakest link in this chain.[4] It was also recognized that polyethylene wear particles contributed, among other things, to a thickening of the soft tissue layer and, therefore, to implant loosening. In dentistry, a direct correlation exists between the thickness of the soft tissue interlayer, the mobility of the implant, the pocket depth of the gingiva surrounding the implant, and the probability of implant failure.[5] At that time, it was generally assumed that a basic cause for the formation of the soft tissue interlayer was the chemical instability of the materials used, mainly the stainless steels, cobalt-based alloys, and the PMMA. This instability resulted in solution products (metal ions or monomers) disturbing the highly sensitive differentiation processes necessary for undisturbed bone formation.

The particular type of ceramic biocompatibility raised hopes of avoiding such soft tissue interlayers and thereby achieving direct anchorage of implant devices. Soft tissue free implant fixation was termed osseo-integration. For joint replacements, the low friction and high wear resistance of alumina ceramics offered an additional advantage.

2. Bioinert Ceramics

The main representative of the bioinert materials is the high purity, high density alumina ceramic. Other oxide and mixed oxide ceramics have also been tested for their biological responses but were found only to approach the compatibility and the other favorable combination of properties of the alumina ceramic.[6,7]

Soon after the early publications several groups extended and detailed the studies of these new materials in different directions: *Boutin*[8] immediately commenced clinical trials and, thus, was the first to insert a hip prosthesis containing an alumina ceramic component into humans, and *Griss* and *Heimke*, as summarized in a review,[9] began detailed studies of the tissue reactions and the possibilities for cement-free anchorage of hip joint components.

Their initial experiments, in which the test pieces were placed in the bony tissue under nearly load-free conditions, confirmed the high degree of tissue compatibility of high-purity alumina and the adequacy of the definition of the term "bioinert" given in Table 1. It was recognized that the reorganization of the bony tissue adjacent to an alumina implant follows exactly the same sequence of reactions characteristic of fracture healing. Further experi-

Table 1. The concept of a bioinert material.

Requirement	Result
"Nothing goes into solution": leakage of ions or other matter from the implant into the surrounding tissue below detectability by the cells and without any systemic effects	No biochemical influence on cell differentiation and proliferation No biochemical information to the cells about the presence of the implant
Strong and fast absorption of molecules contained in body fluent so that the surface of the implant is completely covered (coated) by the body's own matter	No enzyme reactions The implant is "camouflaged" against the host's immune system No foreign body reactions

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ments with fully functional total hip replacements in sheep and dogs revealed the influence of an incompletely stable initial implant fixation and enabled the design criteria to be defined, allowing for a stable and reliable anchorage of the joint components in the adjacent bony tissue. Simultaneously, alumina wear particles were tested biologically as well as the carcinogenicity of this material.[9]

The essential biomechanical requirement for fracture healing is to avoid any shear motion along the interface. In addition to fracture healing, however, it was found that, for maintaining the close bone contact with such a bioinert prosthesis, it is essential to preserve this condition of motionlessness along the interface concerned for the entire lifetime of the prosthesis.

Basically, there are only two mechanical situations allowing for a motionless contact: the load-free situation and an orientation of the interface perpendicular to the forces acting along this interface. Thus, all load-bearing implants must present to the adjacent bony tissue sufficiently large interfaces that are transmitters of mostly pure pressure. Surfaces along which the forces are mainly transmitted parallel (resulting in shear along the interface) are separated by a soft tissue interlayer from the surrounding bone and therefore cannot contribute to osseo-integration and load transmission. Figure 1 summarizes this concept schematically. Clinical experience has shown that the requirement of perpendicularity of the forces meeting the interface allows for a deviation of up to $\approx 15°$.

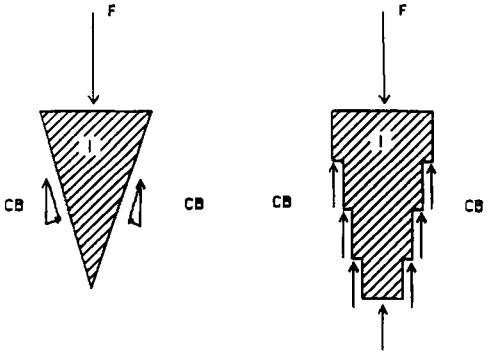

Fig. 1. Schematic representation of the shape dependence of the forces (F) acting along the interfaces of implants (I). Left: large tangential component resulting in shear along the interface; right: pure pressure at the surfaces of the steps, avoiding tangential movements along these surfaces (CB = cancellous bone).

The validity of the concept of the purely stress-and-strain-field controlled tissue reactions along the interface to implants of a bioinert material like Al_2O_3 ceramic was confirmed by the discovery of the "load-line-shadow effect" by *Büsing* et al.,[10] in 1979. The essentials of this effect are schematically described in Figure 2.

According to the previously described requirements for close bone contact, such contact could not be expected along mainly tangentially loaded interfaces such as the cylindrical surfaces of the Tübingen dental implants shown in Figure 3. However, evaluation of the tissue surrounding two implants, which had been in situ and functioning well for many years and which became available for inspection because of an accident the patient suffered, revealed a close bone apposition not only along the pressure transmitting interfaces (the surfaces of the steps connecting the cylinders of different diameters) but also along the cylindrical, mainly tangentially loaded areas. Because of the interlocking effect, due to the presence of the lacunae, and because of the much higher stiffness of the implant as compared with the surrounding, mostly cancellous bone,

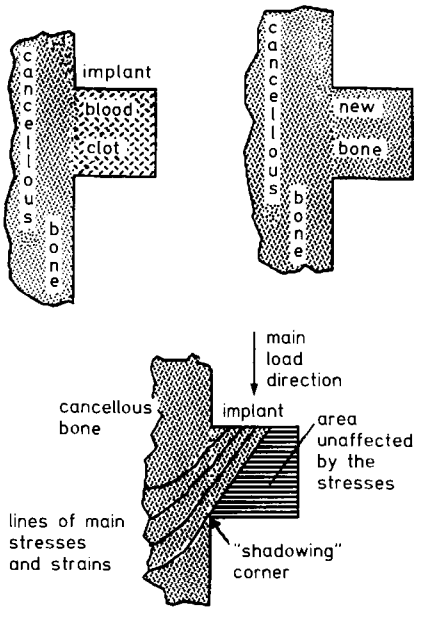

Fig. 2. The Load-Line-Shadow Effect. Top left: after press-fitting the implant, the lacunae are filled with a blood clot. Top right: during the healing-in phase the blood clot serves as a scaffold for new bone formation, filling the lacunae homogeneously. Bottom: After loading, the bony tissue reorganizes according to the stress and strain field present, resulting in an area of decalcification where no stresses are acting, the area which is "shadowed" from the load lines.

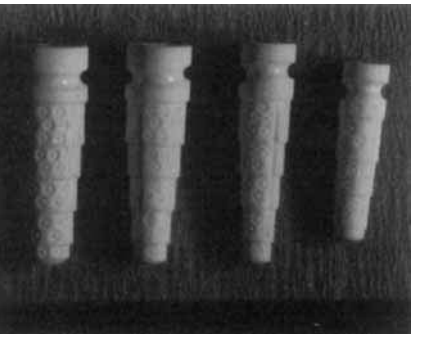

Fig. 3. Frialit Dental Implant, Tübingen type, made of medical grade alumina ceramic. Note the stepped shape of the intraosseous portion with lacunae along the cylindrical surfaces. The grooves parallel to the axis are for additional rotational stabilization. The circular groove around the coronal part is to accommodate the margin of the gingiva.

the relative movements created by all load changes are accommodated by the elastic deformation of these bony structures some distance from the surface of the implant rather than by shear movements along the interface. Thus, an interdependence exists between the shape of the implant and the reactions of the bony tissue surrounding it. To achieve a stable and reliable osseo-integration, the shape of the implant must be chosen so that the stress and strain field created by its insertion allows for remodeling reactions resulting in a close bone contact along as many interfaces as possible.

3. Bioactive Ceramics

A fascinating bond formation was observed between bony tissue and some Ca-phosphate containing glasses and glass ceramics. It was studied in detail by *Hench* et al.[2] and *Blenke* et al.[11] Some time after the insertion into bony tissue, the formation of a silica rich zone along the interface was observed from which some sodium, calcium and phosphate ions had obviously leached out. It was hoped that this zone would act as a diffusion barrier, preventing the leaching out of these ions from continuing. The mechanical strength of the interface in tension or shear was tested after the animals were sacrificed; high forces were needed and the samples mostly ruptured inside the glass or the bone. This mechanically strong bond was found after a healing-in period during which the condition of motionlessness along the interfaces, as in fracture healing, was observed. It was maintained under loading conditions as long as the forces transmitted through the interfaces concerned were mainly perpendicularly oriented, as was the case in the early experiments of *Hench* et al.[2] Along mainly tangentially loaded interfaces, however, the bond could not be maintained reliably. It appears that the silica-rich layer is disturbed again and again by shear forces, resulting in a continuation of the leaching process.

A similarly strong attachment of bony tissue had been observed with some Ca-phosphate ceramics by the mid-1970's. The details of bonding, however, were found to be very different from the bond to the glasses. A summary of information gained after the first decade was given by *Jarchow*[12] and *de Groot*.[13] The main representatives of these bioactive ceramics are hydroxylapatite $Ca_{10}(PO_4)_6(OH)_2$, which, with some variations, is identical with the mineral phase of bony tissue and tricalciumphosphate $Ca_3(PO_4)_2$; this can, with some approximation, be regarded as the dehydrated version of hydroxylapatite. Both materials have been tested biologically in dense and porous versions.

If inserted into bony tissue, a layer of body deposited hydroxylapatite covers most of the implant surface relatively early during the healing-in period. The crystals immediately underneath appear to have lost much of their integrity; organic matter can be detected down to a depth of several crystal layers along grain boundaries.[14] In areas not in contact with bony tissue, the initial resorption processes which also precede the deposition of the bony layers do not cease. The influences of the chemical and phase compositions, crystal structure, and ceramic processing parameters on the tissue responses have been evaluated by several groups. Dense hydroxylapatite and tricalciumphosphate ceramics were found to be relatively stable in the bony environment; for the porous versions, different resorption rates have been found.

The present state of knowledge about the reactions of these bioactive materials in the body environment can be presented in the following three statements:

a) The initial flexural strength cannot be increased to much more than 100 MPa for the Ca-phosphate ceramics and to 200 MPa for the glasses.[15]
b) In the body environment the strength is reduced considerably by corrosion and fatigue.
c) The bond of bony tissue to dense hydroxylapatite can withstand several years of functional loading by shear forces.

4. Clinical Applications of Ceramics in Medicine

The low mechanical strength of the bioactive ceramics and its further reduction by fatigue excludes their uses in most of the load bearing applications. A clinical trial in which the low mechanical strength is believed to be compensated by pre-compressing the hydroxylapatite ceramic of cylindrical dental implants is, with some various after early failures from other reasons, still in progress.[13]

Many attempts have been made to compensate for the poor mechanical properties of these bioactive materials by coating them onto high strength substrates in order to use the bone bonding ability of the bioactive ceramics for the

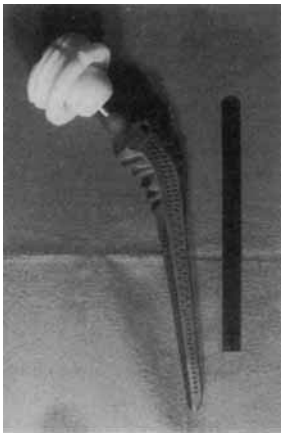

Fig. 4. Frialit Total Hip Replacement System: the cylindrical socket is made of the alumina ceramic as specified in the last column of Table 2. Its threads with asymmetrical cross section are designed for load transmission predominately by pressure. The BMO (biomechanically optimized) stepped stem is made of a TiAlFe alloy.

fixation of joint replacements and other load bearing implants. As the instability of the glasses and glass-ceramic under shear loading was already realized in the late 1970's, much hope concentrated on more or less dense hydroxylapatite coatings. However, here too, the lack of stability of this material in body environment is a fundamental problem, and all experts in this field agreed nearly unanimously during the 3rd World Biomaterials Congress in Kyoto, Japan, in April 1988 that even the best coatings of this kind will not last for more than about six years. They might contribute to the early healing process, but such coatings cannot replace mechanical fixation means like those shown in Figure 4 in long term implants.

The clinical applications of these bioactive materials are, therefore, confined to load-free or nearly load-free situations such as alveolar ridge augmentations, filling of periodontal defects, filling of cysts and other cavities, or corrections in the field of maxillofacial surgery.

The highly dense and pure alumina ceramic has been used in several high load-bearing applications for nearly two decades. No other ceramic has such a favorable combination of properties. The high-strength zirconia ceramics are multiphased, with at least one phase having reduced corrosion resistance. The essential properties of the medical-grade versions of the alumina material had been standardized during the 1970's (ISO 6474, ASTM F 603-83, DIN 58835). Extended clinical experiences have shown, however, that further improvements are necessary to extend the safety margin. The combination of properties that has been reached with a specially tailored material is shown in Table 2 and compared to the standard values.

Table 2. Properties of medical-grade alumina ceramics.

Property	Ceramic according to ISO 6474 ASTM F603-83 DIN 58835	Frialit Bioceramic
Density [g cm^{-3}]	> 3.9	> 3.98
Alumina content [%]	> 99.5	> 99.9
SiO_2 and alkali metal oxides [%]	< 0.1	< 0.05
Microstructure, average grain size [μm]	< 7	< 2.5
Microhardness [MPa]	23000	23000
Compressional strength [MPa]	4000	4000
Flexural strength [MPa]	> 400	> 450
Young's modulus [MPa]	380000	380000
Impact strength [cm MPa]	> 40	> 40
Wear resistance [mm^3 h^{-1}]	0.01	0.001
Corrosion resistance [mg m^{-2} d^{-1}]	< 0.1	< 0.1

4.1. Applications in Orthopedic Surgery

In orthopedic surgery the first ceramic implants whose design takes full account of the stress and strain field controlled bone reactions are the cylindrical sockets of the Frialit Total Hip Replacement system shown in the upper part of Figure 4. They are combined with a ball of the same ceramic fixed on a metal stem. Their clinical trial commenced in 1974. They have now stood the test of more than 14 years of clinical application. The first generation of these sockets and balls had been combined with metal stems which are still anchored with bone cement. Extended further animal experiments led to the design of stems with specially shaped steps and lacunae,[16] shown in the lower part of Figure 4. These stems are made of a vanadium-free high strength TiAlFe alloy tailor-made for medical applications.[17] This now completely cement-free implantable system has stood the test of more than six years of applications in many clinics.

One other hip replacement system with alumina ceramic sockets which also takes approximate account of the design rules mentioned above was introduced into clinical trials shortly afterwards. These ceramic sockets have also proved to be satisfactory.[18]

As already mentioned, some years earlier *Boutin* had commenced the application of alumina ceramic in hip surgery.[8] His design, however, closely followed the shape of plastic cups designed for cement fixation and did not take account of the design rules discussed above. Some years later *Chiari* et al. tested such sockets experimentally and *Plenk* found them to be separated from the bone by a soft tissue layer along most of the interface.[19]

Relatively early alumina ceramic implants were used in tumor surgery of the proximal femur and in the upper arm, but without convincing results.[20] Similarly, early attempts to introduce alumina ceramic components in knee surgery have not led to large scale applications.[21] Extended experiments with ceramic on ceramic articulating knee replacements never reached the state of clinical trials.[22] It was not until the introduction of total knee replacements with anchoring portions and femoral condyles of alumina ceramic and an articulating tibia plateau layer of polyethylene, and of ankle joints with a similar material combination, that ceramic components found clinical application in this part of the lower extremities.[23]

The discovery of a considerable reduction of the polyethylene wear debris in the combination of alumina ceramic balls with polyethylene sockets,[24] as compared to metal balls in the same application, led to large scale uses of this combination in Europe. Long term follow-up studies in many clinics have confirmed that this combination results in a reduction of the polyethylene wear debris by a factor of two.

4.2. Alumina Ceramics in Dentistry

The application of Degussit, a dense alumina ceramic, to dental implantology and other fields of medicine was suggested by *Sandhaus* as early as 1964.[25] The first ceramic dental implant system fully taking into account the remodeling ability of bony tissue was designed by *Schulte* and *Heimke* in 1975 and subsequently tested on a strictly

experimental basis with a detailed follow-up of each single implant. In 1977, following the presentation of the early, two years' results, eleven other clinics of the German speaking countries participated in this clinical study. In 1980 the results achieved were summarized in a special symposium. It was not until this survey was undertaken that these implants were made available to the dental practitioners. A detailed interim report has been prepared.[26]

This implant system (an example of such an implant is shown in Figure 3) allows immediate replacement of an extracted tooth, thus preventing the atrophy of the alveolar ridge with all its later difficulties. It can also be used as a so-called late implant in the already healed and even partially atrophied jaw. A variation of the original design takes special account of this application.[27]

Scientifically, all the different studies (e.g. histology) on retrieved implants, different types of mobility tests, and detailed studies of the gingival attachment either confirmed the initial design rules or, like the discovery of the load-line-shadow effect, even contributed to a more detailed understanding of the load-pattern-controlled tissue reactions around bioinert implants. In addition, the observation of full preservation of the shape of the alveolar ridge around such immediate implants after more than twelve years opens a new regime of dental care with the possibility of considerably improving public health.

A surprising point of view is also worth mentioning, amplifying the statement about dental care. From the definition of the term "bioinert" given in Table 1, mentioning the adsorption properties for body molecules, one would have expected a tendency for increased plaque formation with such ceramic implants. However, experience has shown beyond any doubt that the opposite is true: these implants cause much less plaque formation than metal implants or natural teeth.

The follow-up of all implants inserted in the Tübingen clinic (now more than 1000) has yielded more than one million items of data, which have been computerized and evaluated after five and ten years from all relevant points of view. The average success rate of these implants, if applied within their regime of indications, was 92.5% after five years, and remained so in the ten year analysis.[28]

Besides the *Sandhaus* implant already mentioned, there are other dental implant systems utilizing either alumina ceramic or alumina single crystals. None, however, meet the biomechanical requirements for osseo-integration of bioinert implants. Rather, all of them merely duplicate more or less the shape of the previous metallic implant designs. Therefore, many of these implants are separated from the surrounding bony tissue by soft tissue interlayers having different thicknesses. This soft interlayer, of course, results in implant mobility which, in turn, creates some mechanical irritation of the gingiva surrounding it and increases the probability of infection and implant loss.[5] There exists, however, no large-scale or long-term statistical evaluation on any of these implant systems.

4.3. Applications of Ceramics in ENT and Maxillofacial-Surgery

In the field of ears, nose and throat (ENT) surgery the transmission of forces is of minor importance for most of the large-scale applications. Thus, the bioactive ceramics have found some applications here.

Middle-ear implants of alumina ceramic replacing all or part of the ossicular chain (see Fig. 5) were tested and introduced clinically by *Plester* and *Jahnke*.[29] Almost simultaneously, *Reck*[30] evaluated a Ca-phosphate containing glass-ceramic for the same purpose and reported the formation of a thin bony membrane between the plate of these implants and the tympanic membrane. However, some concern exists about the building of a bony bridge between the bone around the oval window and the shaft of the implant because of its bioactivity. This same danger exists for hydroxylapatite implants suggested for this application.[31] The alumina and the glass ceramic ossicular chain replacements have now stood the test of up to nine years of clinical use.

Fig. 5. Frialit middle ear implants of different shapes for easy adjustment to the individual situation.

Porous tricalciumphosphate ceramics were considered as filling material for different kinds of bone defects by many authors. *Zöllner* et al. used a relative stable material of this kind for the reconstruction of the mastoid and adjacent bone walls.[32] They confirmed the good bone bonding ability of this material, gave indications about its slow degradation, and demonstrated that such materials must not be used in positions immediately below the skin because of the danger of dehiscences.

The same group designed, tested clinically and introduced the alumina ceramic trachea supporting ring shown in Figure 6.[33] It is to replace the cartilage around the trachea if it has to be removed in tumor surgery.

Orbital support plates of alumina ceramic have been tested and clinically introduced by *Frenkel* et al. in the late 1970's.[34]

Many attempts have been made to improve the results of some branches of plastic surgery by the insertion of ceramic spacers. Examples are the attempts of *Swart* and *de*

Fig. 6. Frialit trachea supporting ring.

Groot to change the jaw bone geometry with hydroxylapatite ceramic[35] and of *Wilson* with a bioactive glass.[36]

5. Final Remarks

Of all the ceramic materials considered for implant applications, only a few were found to meet the very severe requirements. The highly dense and pure alumina ceramic has stood the test of more than a decade of clinical use in different fields of surgery, and could eventually find large scale applications in several areas. Only one of the bioactive glasses has reached the state of routine application as ossicular chain replacement. Several Ca-phosphate ceramics have stood the test of nearly ten years of application in dentistry, in particular in alveolar ridge augmentations to improve the stabilization of total dentures.

In spite of the basic, still unsolved problem of its limited stability in the body environment, many attempts are still being made to elicit the favorable biological response to the Ca-phosphate ceramics for the fixation of bone replacements. Increasingly sophisticated composites and multilayer systems are being designed and tested. However, the more complicated the systems become, the higher the probability of failure and the greater the effort necessary to arrive at a well founded decision to commence clinical trials.

One more point needs to be considered: the present day success rates achieved with the already well established systems are to be regarded as the standard that any new system must surpass. Because one is dealing with humans, extremely strong evidence must exist and clearly indicate a high probability of a considerable improvement over existing systems before any clinical trial can be considered at all. Furthermore, any judgement about the success of an intended improvement cannot be given until at least five years of a closely controlled clinical series have been completed.

Received: October 26, 1988

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