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Biocompatibility

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1. Introduction

During the past few years, the biocompatibility of biomaterials (non-vital material intended to interact with biological systems within or on the human body) has evolved into a comprehensive, complex, and independent discipline of biomaterials science. Consequently, a number of terms have been developed or were adopted from toxicology. Some of these terms may be familiar to patients and clinicians from daily life – for example, the term "safety". Safety in relation to the evaluation of biomaterials means freedom from unacceptable risks. Thus, safety does not stand for a complete lack of risks.

2. Biocompatibility

2.1 Definition of biocompatibility

Biocompatibility is a word that is extensively used within biomaterials science, but there still exists a great deal of uncertainty about what it actually means and about the mechanisms that are subsumed within the phenomena that collectively constitute biocompatibility. During the 2nd Consensus Conference in Liverpool, biocompatibility was defined as "the ability of a material to perform with an appropriate host response in a specific application" (Gatti & Knowles, 2002, as cited in 2nd Consensus Conference, 1991). A biocompatible material may not be completely "inert"; in fact, the appropriateness of the host response is decisive. Previously, the selection criteria for implantable biomaterials evolved as a list of events that had to be avoided, most of these originating from those events associated with the release of some products of corrosion or degradation, or additives to or contaminants of the main constituents of the biomaterial, and their subsequent biological activity, either locally or systemically. Materials were therefore selected, or occasionally developed, on the basis that they would be non-toxic, non-immunogenic, non-thrombogenic, non-carcinogenic, non-irritant and so on, such a list of negatives becoming, by default, the definition of biocompatibility. A re-evaluation of this position was initiated by two important factors. Firstly, an increasing number of applications required that the material should specifically react with the tissues rather than be ignored by them, as required in the case of an inert material. Secondly, and in a similar context, some applications required that the material should degrade over time in the body rather than remain indefinitely. It was therefore considered that the very basic edict that biocompatibility, which was equated with biological safety, meant that the material should do no harm to the patient, was no longer a sufficient pre-requisite. Accordingly, biocompatibility was redefined in 2008 as "the ability of a material to perform its desired function with respect to a medical therapy, without

eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimizing the clinically relevant performance of that therapy" (Williams, 2008).

2.2 Components of biocompatibility

In addition to the beneficial tissue response and the clinically relevant performance of a biomaterial, cytotoxicity, genotoxicity, mutagenicity, carcinogenicity and immunogenicity are considered to be the components which constitute "biocompatibility" (Table 1).

Beneficial tissue response and the clinically relevant performance
Cytotoxicity (systemic and local)
Genotoxicity
Mutagenicity
Carcinogenicity
Immunogenicity

Table 1. Components of biocompatibility

Toxicity of a material describes the ability to damage a biological system by chemical means. In higher organisms (animals, human beings), local toxicity – that is, adverse reactions emerging at the application site – is differentiated from systemic toxicity, in which adverse reaction appear in an area distant from the application site. Cytotoxicity refers to damage to individual cells, for example in cell cultures. Cells can die because of necrosis or apoptosis (programmed cell death).

Immunogenicity is referred to the ability of a substance to provoke an immune response or the degree to which it provokes a response. An allergic reaction to a substance can be triggered if the organism was previously sensitized to this substance. The concentrations that elicit a reaction in a previously sensitized person vary between subjects. The dose levels causing allergic reactions are generally significantly lower than those causing toxic reactions.

Genotoxicity describes an alteration of the basepair sequence of the genome DNA. Cells possess numerous mechanisms to repair genotoxic damages. Alternatively, a transfer of these genetic damages to subsequent generations of cells can be avoided by programmed cell death (apoptosis). Nonetheless, if theses genetic damages are passed on to the next generation, this effect is called mutagenicity. Mutagenicity and carcinogenicity are not the same. Carcinogenicity means that alterations in the DNA have caused a cell to grow and divide inappropriately; in other words, alterations of DNA promoted the generation of malignant tumors. Carcinogenicity results from several mutations. It is important to understand that not all mutagenic events lead to carcinogenesis. However, mutagenicity can be assessed as an indicator of "possible" carcinogenicity of substances that directly attack DNA.

The components of biocompatibility will be discussed in relation to bioceramics later in the current chapter.

3. Bioceramics

3.1 Definition of bioceramics

In practical sense, the term bioceramics can be referred to a group of ceramics, which are used in the field of biomedicine. These biomaterials are ceramics, which are manufactured or processed to be suitable for use in or as a medical device that comes into intimate contact with proteins, cells, tissues, organs, and organ systems.

3.2 Benefits and clinical performance of bioceramics

Bioceramics are used to restore normal activity of diseased or damaged parts of the body. As people age, progressive deterioration of tissues requires replacements in many critical applications. After successful researches, various bioceramic products are now commercially available in the medical market as substitutes for the original damaged body parts and for many other critical applications (Table 2).

Dentistry	Dental restorations
	Prosthodontic devices
	Orthodontic brackets
	Repair of periodontal disease
	Maxillofacial reconstruction
Orthopedics	Joint replacements
Cardiology	Prosthetic heart valves
Neurosurgery	Cranioplasty repair
Otolaryngology	Middle ear implants, Vocal cord paralysis
Miscellaneous	Magnetic treatment of bone tumors
	Drug delivery systems

Table 2. Benefits of ceramics in biomedicine.

Traditionally, ceramics have seen widescale use as restorative materials in dentistry. Dental ceramics are rigid materials that are shaped by sintering, casting, pressing, milling, or sonoerosion. Dental ceramics are also available as prefabricated inlays (inserts). Dental ceramic restorations include materials for denture teeth, fixed partial dentures, full crowns, veneers, inlays, onlays, and post - cores to restore missing tooth part, a tooth, or teeth. Restorative dental ceramics could be bonded to metal (Metal-Ceramics) or be metal free ceramics (All-Ceramics). High-performance ceramics yield excellent technical properties, which make them suitable to be used as copings or frameworks for crowns and bridges. To improve their aesthetics, they have to be veneered with other, mainly silicium oxide

ceramics. Dental ceramics are further applied as implant materials, for example as coating for titanium implants, or as full ceramic implants. The most recent use for ceramics in dentistry is orthodontic brackets. The development and demand for these items has been driven solely by aesthetics. Also, ceramics are used for repair for periodontal diseases. They are also useful for maxillofacial reconstruction, augmentation and stabilization of the jaw bone because bioceramics may develop the clinical applications of bone substitutes. The physical, chemical and biological properties of bioceramics can be used for preparing advanced bone substitutes. Bioactive glass ceramics and calcium phosphate ceramics are the two ceramic types used as bone substitute or for bone healing process. Bioactive glass ceramics bonds to bone without an intervening fibrous connective tissue interface (Schepers et al., 1991). When granules of bioactive glass ceramics are inserted into bone defects, ions are released in body fluids and precipitate into a bone-like apatite on the surface, promoting the adhesion and proliferation of osteogenic cells (Neo et al., 1993). After long-term implantation, this biological apatite layer is partially replaced by bone (Neo et al., 1994). Bioactive glass with a macroporous structure has the properties of large surface areas, which are favorable for bone integration. The porosity provides a scaffold on which newly-formed bone can be deposited after vascular ingrowth and osteoblast differentiation. The porosity of bioactive glass ceramics is also beneficial for resorption and bioactivity (De Aza et al., 2003). Calcium phosphate polycrystalline ceramic materials can be produced by precipitation from aqueous solutions and by solid-state reactions. The rationale for using hydroxyapatite as a biomaterial is the advantage of using a material having similar composition and crystalline structure as natural calcified tissues. Hydroxyapatite and other calcium-based ceramic materials can actively encourage bone regeneration at the surface of an implant. It has been postulated that the use of calcium phosphate ceramic biomaterials might replace the use of bone grafts. The chemistry of these materials is reasonably well established (Nascimento et al., 2007) and significant animal experiments have shown these materials to be both biocompatible and bioactive.

However, bioceramics use in other fields of biomedicine has not been as extensive, compared to metals and polymers. For example, in orthopedics, ceramics such as alumina (aluminum oxide ceramics) and zirconia (zirconium oxide ceramics) are used for wear applications in joint replacements. Bioceramics can now be used for hips, knees, tendons and ligaments replacements. In cardiovascular or circulatory system (the heart and blood vessels involved in circulating blood throughout the body), problems can arise with heart valves and arteries. The heart valves suffer from structural changes that prevent the valve from either fully opening or fully closing, and the diseased valve can be replaced with a variety of substitutes. As with dental implants, ceramics may be used as pyrolytic carbon coatings for prosthetic heart valves (Sarkar & Banerjee, 2010). Less obvious examples of the use of ceramics as biomaterials are in neurosurgical cranioplasty repair of the skull bone defects, in hand arthroplasty of the metacarpophalangeal joint, in otolaryngology as implants in the middle ear, or the use of bioactive glass ceramics in the treatment of vocal cord paralysis. Bioactive glass ceramics containing magnetite can be used to kill bone tumors when a magnetic field is applied. Ceramics implants can also be used as drug delivery systems (Nascimento et al., 2007).

3.3 Classification of bioceramics

Based on their chemical reactivity with the physiological environment, bioceramics can be broadly categorized in three types (Fig. 1):

3.3.1 Bioinert ceramics

They are such as alumina, result in little or no physiological reaction in the human body and tend to exhibit inherently low levels of reactivity which peak in the order of hundreds of years. They are attached by compact morphological fixation.

3.3.2 Surface reactive or bioactive ceramics

They are such as bioactive glass ceramics (bioglass), react in a positive way with local cells, i.e. they directly attach by chemical bonds and have a substantially higher level of reactivity, peaking in the order of 100 days.

3.3.3 Resorbable bioceramics

They are porous or nonporous structures which are slowly and gradually replaced by bone such as tricalcium phosphate, have even higher levels of reactivity, peaking in the order of 10 days (Shackelford, 2005).

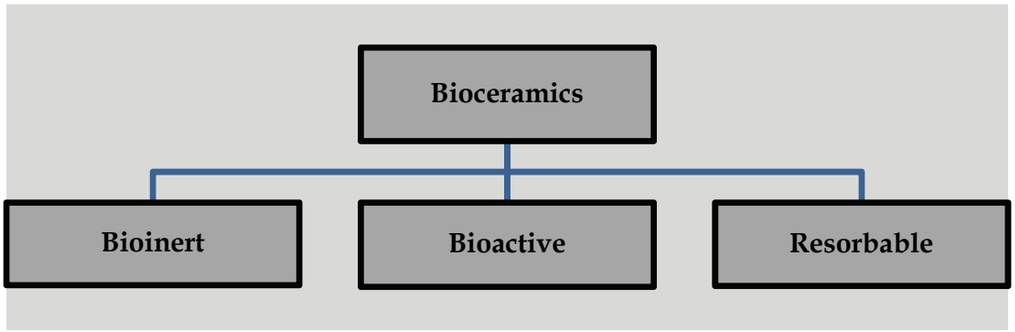

Fig. 1. Classification of bioceramics according to biocompatibility

4. Why is it significant to study biocompatibility of ceramics?

Biocompatibility of ceramics is a critical issue because of three different reasons. The first is that these materials are in intimate contact with human tissues for long terms and cannot be removed by the patient. Secondly, biocompatibility is an ongoing process and not a static one. For example, it is possible that a dental implant that is osseointegrated today may or may not be osseointegrated in the future. Thirdly, it has to be stressed that biocompatibility of fixed prosthodontic materials like ceramics is often overlooked because many practitioners assume that, if the material is on the market, its biocompatibility does not need to be questioned. For example, two systems are currently responsible for standards that can be used to document dental products quality: the American National Standard Institute / American Dental Association (ANSI/ADA) document No. 41 (1997) and addendum No. 41A (1982) and the International Standards Organization (ISO) 10993 document (1993). The ANSI/ADA and ISO do not require specific biologic tests to approve the quality of a new dental material. Rather, they place the responsibility on the manufacturer to present evidence for a compelling case for approval. So, it is up to the manufacturer to defend the substantial equivalence argument. The evidences used for approval of quality of a dental material consist of in vitro tests (cell-culture), in vivo tests (animal experiments), and clinical tests (clinical trials of the material). However, it is becoming increasingly impractical to test all new materials through all of these stages. The problems of time, expense, and ethics have

limited the usefulness of this traditional biologic testing scheme. Therefore, companies market materials with little clinical experience, and may rely heavily on in vitro and animal experiments (Wataha, 2001).

Although most ceramic materials are generally regarded as being more or less inert, their possible effects of degradation products on biological systems must not be overlooked. The composition and physical properties of ceramic materials can affect the inertness. Safety cannot be inferred from measurements of one ceramic formulation to other compositions or conditions. Since bioceramics have been mainly used in dentistry, biocompatibility and its relevant properties for ceramics will be mainly discussed in relation to oral health.

5. Biologically relevant properties

5.1 Ceramics composition

It is believed that biologic reactions in general are mainly based on the interaction of a substance eluted from a material with a biologically relevant molecule. Thus, the composition of a material is of importance for its biocompatibility (Schmalz & Garhammer, 2002). Different elements in the periodic table of elements can be used in ceramics. The diversity of these ceramics makes understanding their biocompatibility difficult, because any element in a material may be released and may influence the body.

Ceramics are commonly described by their composition. However, composition can be generally expressed in two ways; either as weight percentage (wt %) of elements or percentage of the number of atoms of each element in the material (atomic percentage = at %). Weight percentage is the most common way of describing a material's composition, and is used by material manufacturers and by standard organizations. However, biologic properties are best understood by knowing the atomic percentage composition. Atomic percentage better predicts the number of atoms available to be released and affect the body. The wt% and at% of a material or an alloy may be substantially different from each another.

Ceramics could be oxide or non-oxide ceramics. Oxide ceramics in dentistry are primarily based on silicon oxide (SiO_2), aluminum oxide (Al_2O_3), and zirconium oxide (ZrO_2). Non-oxides, such as silicon carbide, silicon nitrite, and aluminum nitrite, are of minor importance in dentistry due to their black color. Some dental ceramics can be combined, such as an Al_2O_3-ceramic framework veneered with SiO_2 ceramic. Lanthanum glass is used as a coupling agent, which infiltrates the aluminum oxide framework. Lanthanum glass consists of 39% lithium oxide. Additives (such as leucite) are intended to improve the mechanical properties of the ceramics, in particular to limit crack propagation. Further additives in dental ceramics are fluxing agents and coloring pigments, such as metal oxides, as well as fluorescents such as oxides of cesium and samarium. Some calcium phosphate materials are regarded as ceramics, too. These substances represent a very heterogeneous group of materials, including sintered hydroxyl apatite (HA) with a very low solubility and tricalcium phosphate (TCP) ceramics with varying resorption behaviors. Calcium phosphate ceramics usually consists of 100% of the respective mineral phase (TCP or HA).

5.2 Biodegradation and corrosion

Biological systems may have harmful or destructive effects on bio- materials, classified as biodegradation. In the oral environment, this includes not only the process of destruction and dissolution in saliva but also chemical/physical destruction, wear and erosion caused by food, chewing and bacterial activity. Therefore, it is important to evaluate the material

reactivity in the oral cavity, which is governed by thermo-dynamic principles and electro-chemical reaction kinetics. This means that when a material is placed in the oral cavity, the material-saliva system will be driven toward a state of thermo-dynamic equilibrium. At equilibrium, the material either will remain stable in its elemental form or oxidize into its ionic form (corrosion). Thus, the initially uncharged elements inside the material lose electrons and become positively charged ions as they are released into solution. Corrosion is a chemical property that has consequences on other material properties, such as esthetics, strength, and biocompatibility. From a biocompatibility standpoint, the corrosion of a material indicates that some of the elements are available to affect the tissues around it.
The chemical durability of dental ceramics is basically good. They are commonly regarded as insoluble or only very slightly soluble at best. However, the degradation of dental ceramics can generally occur because of mechanical forces (wear) or chemical attack (solubility in an acidic, neutral, or alkaline environment), or a combination of the two. Some calcium phosphate ceramics are internationally engineered for a gradual resorption (TCP). The release of substances can generate unwanted effects (biological and mechanical) on one hand, or it may promote biocompatibility on the other hand, such as in terms of improved bone apposition (bioactivity). The multiphase microstructure of many dental ceramic materials results in complicated corrosion modes, as each phase is likely to react individually to the corrosive medium. Besides, chemical durability of ceramic materials may be influenced by many other factors, such as the chemical character of the corrosive medium, the exposure time, and the temperature. For glass ceramics, the initial surface reaction is mainly an acid-base reaction in which leaching ions are replaced by H^+ ions, the result of which will be an alkali-ion-depleted leach layer overlying a permeable gel layer. Beneath the alkali-depleted layer, the corrosion process will produce a silica-rich layer, offering some protection to the bulk material. However, because of differences in composition, microstructure, and local corrosion conditions, the corrosion process is far more complicated and may also lead to the partial breakdown of the silicate structure at the surface. In addition, glasses high in K_2O have been less chemically durable than glasses made with soda (Na_2O) as an added flux material, whereas the presence of zirconia and alumina has shown to improve the chemical durability of glasses. When exposed to hydrolysis testing, ultra-low-temperature sintering ceramics displayed higher solubility than traditional high-temperature sintering ceramics. However, in repeated hydrolysis tests, high- and low-sintering ceramic materials did not react in the predicted manner. Alumina, which is regarded as a very stable material, may also undergo compositional changes when exposed to a corrosive environment (Milleding et al., 2002).

5.3 Ion release

Corrosion, as mentioned before, is always accompanied by a release of elements and a flow of current. The release of substances from dental materials is considered to be gradual and to occur in small amounts. Evaluation of mass release from dental ceramics is not common in the literature, although there are some studies that have demonstrated such mass release. The leakage of inorganic ions from ceramics has been found to take place in aqueous media and vary with the glass composition and environmental conditions. Under more severe conditions (as the concentration of alkali ions increases), the Si-O-Si bonds may be broken, and the entire glass structure may be impaired. The reduction in chemical durability is of importance, since an increased susceptibility to chemical attack may release ions of the elements (K2O.Al2O3.4SiO2), which in certain circumstances, could be considered undesirable from a biocompatibility perspective (Milleding et al., 2002).

Two dominant mechanisms could be responsible for the aqueous corrosion of alkali-silicate glasses: (1) the selective leaching of alkali ions and (2) the dissolution of the glass network. At a pH of 9 or less, selective leaching of alkali ions could be the dominant mechanism. This mechanism can be controlled by the diffusion of H^+ or H_3O^+ ions from an aqueous solution into the glass and the loss of alkali ions from the glass surface. In general, alkali metal ions from glass are much less stable in the glass phase than in the crystalline phase and thus could be leached more rapidly.

In contact with saliva or other organic fluids, biomaterials are instantly covered with organic films, the composition and properties of which undoubtedly influence the surface corrosion process and subsequent bio-reactions. It has been assumed that organic films on ceramic surfaces reduce the surface degradation by building up concentration gradients and reducing the diffusion of ionic elements through the surface films. In addition, it has been found that leaching of inorganic ions can be influenced by pH of the corrosion solutions and the ions potential for the complex binding of dissolved glass constituents, resulting in more extensive corrosion than indicated by the pH value alone (Milleding et al., 2002).

Sjögren et al. (2000) tested the release of elements from different dental ceramics (low-fusing, conventional veneering, press-casting ceramics) into a cell culture medium by inductively coupled plasma optical emission spectrophotometry. They found multiple released elements such as aluminum (Al), silicon (Si), sodium (Na), potassium (K), magnesium (Mg), and calcium (Ca). Also, Milleding et al. (2002) studied the in vitro ion dissolution from glass-phase ceramics, with or without crystalline inclusions, and from all-crystalline ceramics using the inductively coupled plasma optical emission spectroscopy. A large number of inorganic elements leached out from the previous dental ceramics. The major leaching elements were sodium and potassium. There were also magnesium, silicon, and aluminum. The various glass-phase ceramics displayed significant differences in ion release and significantly higher release values than all-crystalline alumina and zirconia ceramics. No significant difference in dissolution was found between high and low-sintering glass-phase ceramics or between glass-phase ceramics with high volume fractions of crystallites in the glass phase in comparison with those with lower crystalline content.

Logically, it has to be noted that the type of released elements depends on the composition of ceramic material itself. From silicon oxide ceramics, silicon, sodium, potassium, boron, and aluminum are released into various diluents at different pH values; silicon, sodium, and potassium are leached in higher amounts than are aluminum and boron. Aluminum oxide ceramics leach only minimal amounts of ions under physiological conditions. Calcium phosphate ceramics release calcium and phosphate into adjacent tissues. Overall, hydroxyapatite and fluorine apatite ceramics are less soluble than tricalcium phosphate ceramics (Lacefield, 1999).

6. Types of biocompatibility tests

Biomaterials are developed in order to evaluate, treat, augment or replace human tissue, organ or function. Biocompatibility is the main prerequisite for their safe use as medical devices. In order to assess the biocompatibility of a material, it is necessary to do a battery of tests, depending on the intended use, location and duration the material is to come in contact with the tissues. The evaluation of biocompatibility is dependent not only on the tested biomaterial but also on the test method used. So clinicians need to be familiar with these methods. Biocompatibility is measured with 3 types of biologic tests: in vitro tests, animal experiments and clinical tests (Fig. 2).

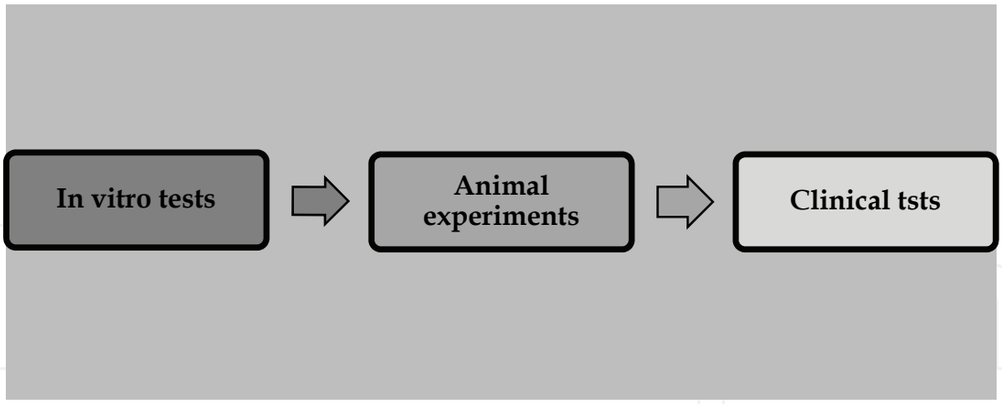

Fig. 2. Plan of biocompatibility tests in order.

The common approach when testing the biological behavior of materials is to start with simple in vitro tests. If these experiments and investigations of a material's efficiency deliver promising findings, then more comprehensive studies on experimental animals (in vivo evaluation) will be performed. Clinical trials (usage tests) are the final step of this evaluation process.

6.1 In vitro tests

In vitro biocompatibility tests are less expensive ways to survey newly developed materials. They simulate biological reactions to materials when they are placed on or into tissues of the body**.** These tests are performed in a test tube, cell-culture dish, or otherwise outside of a living organism in which cells or bacteria are generally placed in contact with a material. For example, a strain of bacteria may be used to assess the ability of a material to cause mutations (the Ames test). The advantages of in vitro biocompatibility tests are, being experimentally controllable, repeatable, fast, relatively inexpensive and relatively simple. Another major advantage is that these tests generally avoid the ethical and legal issues that surround the use of animals and humans for testing. The primary disadvantage of in vitro biocompatibility tests is their questionable clinical relevance.

6.2 Animal experiments

In animal experiments, the material is placed into an animal, usually a mammal. For example, the material may be implanted into a mouse or placed into the tooth of a rat, dog, cat, sheep, goat or monkey. Animal models allow the evaluation of materials over long time durations and in different tissue qualities (e.g. normal healthy or osteopenic bone) and ages. Not only can the tissues in the immediate vicinity be assessed, but, tissues in remote locations of the implanted material can also be studied, which is particularly relevant to the study of wear particle debris. However, questions arise about the appropriateness of an animal species to represent the human response and that they are time-consuming and expensive. In animal experiments, ethical concerns and animal welfare issues are very important.

6.3 Clinical tests

The clinical test is, by definition, the most relevant biocompatibility test. These tests are essentially clinical trials of a material in which the material is placed into a human volunteer

in its final intended use. In a controlled clinical study, test and control materials are examined at the same time. Controlled clinical studies possess a higher level of significance/evidence compared with studies in which only one material is investigated. Biocompatibility data from clinical studies are naturally of special interest for the clinician, since the examination was done on the target group of this material (patients). But this should not conceal the fact that clinical studies reveal limitations, too. An uncritical transfer of such results to patients in daily practice may result in problems, for instance, if data are not based on a blinded study. Therefore, at least treatment and subsequent assessment should be done by different persons. Many unwanted reactions appear only after chronic exposure. But clinical studies – in particular those with new materials – are frequently limited to comparatively short periods of time (some are only 6 months). In addition, only a small and often strictly selected group of patients is included in the study, for instance in a university hospital. The clinical studies are also expensive, time-consuming, extraordinarily difficult to control its variables, difficult to interpret and may be legally and ethically complex. Clinical tests are done only if satisfactory results are obtained in the in vitro and animal experiments.

7. Systemic toxicity

7.1 Means of systemic toxicity testing

Experimental animals are usually used to determine systemic toxicity. Previously, the acute lethal dose 50% (acute LD_{50}) was determined as routine. Acute LD_{50} is the dose required to kill half the members of a tested population after specified test duration. Today, other methods that are more sparing of animals are used, such as the so-called limit test (administration of a fixed dose, e.g., 2,000 mg/kg body weight). The chronic systemic toxicity will be determined by administering the material or extract over several months. Tests are sometimes extended over the lifetimes of the experimental animals. At the end of these studies, survival rates of the animals and patho-histological alterations of the main organs will be determined. Further information regarding chronic toxicity is obtained from accidents (high exposure level) and based on observations of occupationally exposed subjects (e.g., dental personnel) who are often in contact with the “active” unset material.

7.2 Systemic toxicity related to ceramics

One fundamental concern about the safety of ceramics used as fixed prosthodontic materials is their ability to cause systemic toxicity in the body. A stress must be applied on several key concepts that affect this concern. For example, in dentistry, the following should be concerned (Wataha, 2000):

7.2.1 Presence inside the body

Elements released from a dental fixed prosthodontic material into the oral cavity are not inside the body because these elements may gain access to the inside of the body through absorption in the gastrointestinal tract, in the oral mucosa, from the skin, or in the respiratory system. The mechanism for this absorption depends on the nature of the chemical properties of the released elements - whether they exist as ions, as hydrophilic and lipophilic compounds, as volatile substances, or as particles. In contrast, elements that are released from dental implants into the bony tissues around the implant are, by definition,

inside the body. Therefore, elemental release from ceramic implants is thought to be more critical systemically than elemental release from dental ceramics used for prosthetic restorations.

7.2.2 Route of access to the body

The route by which an element gains access inside the body is critical to its biological effect. Some elements become more toxic when administered intravenously into mice than when administered orally.

7.2.3 Distribution in the Body

Any biomaterial, once inside the body, can release ions which can be distributed to many tissues by diffusion through tissues, the lymphatic system, or the blood stream. Released metallic particles (0.5 to 10.0 um) may also be ingested by cells such as macrophages. Almost all dental materials release substances into the oral cavity, from where they may enter the human body through different routes, including swallowing of saliva and inhalation, with subsequent passage of the epithelial barriers in the gastrointestinal tract or the lungs. These substances may, via the blood circulation, be transported to different organs. The oxidation state and chemical form of the metallic ions will significantly influence its absorption, distribution, retention half-life, and excretion. Ultimately, the body generally eliminates the released ions through the urine, feces, or lungs. The application site may thus be in a different location from the effect. At the location of the effect, there may be interference with the function of the specific organ if the concentration is sufficiently high (systemic toxicity). According to the time frame, acute (up to an exposure period of 24 h), subacute (up to 3 months), and chronic toxicity are differentiated.

In general, the systemic toxicity of ceramics is considered to be extremely low (Aldini et al., 2002). In dentistry, only dental laboratory technicians might be exposed to an inhalation of ceramic dust due to processing and finishing of dental ceramics that may cause silicosis (fibrotic pneumoconiosis). These lung diseases have been observed in workers in the ceramic industry who were exposed to ceramic dust for an extended period of time. The risk to a dental laboratory technician of developing silicosis due to ceramic dust is currently unknown. The patient's silicosis risk is considered "very minimal" (Mackert, 1992) if commonly accepted safety measures, such as dust removal, are followed. On the other hand, there is evidence that released metallic ions from fixed prosthodontic materials can and do gain access to the body, and these metallic ions may be widely distributed (Wataha, 2000). Person-Sjögren & Sjögren (2002) found a statistically significant increase in levels of insulin release from the Langerhans cells after exposure to lithium-containing ceramic (Empress ceramics). The danger lies in overseeing the possibility that minimal amounts of ions eluted due to chemical or mechanical wear might adversely affect the pancreas, or other organs or tissues.

8. Local toxicity

8.1 Means of local toxicity testing

Current knowledge about biomaterials-tissue interactions has been gained through bioassays in vitro and in vivo. Taking into account biocompatibility tests available in the

general field, cytotoxicity assays are of special concern. In vitro studies are mainly performed to evaluate the cytotoxicity. A vast number of different in vitro test methods exists which include both quantitative and qualitative methods of cytotoxic effect, i.e. cell damage or lysis caused by membrane leakage. However, each test method basically consists of three components: (a) the biological system, (b) the cell/material contact, and (c) the biological endpoint and corresponding recording system. The biological system used in in vitro cytotoxicity tests may be (i) organ cultures, (ii) cells in culture or (iii) cell organelles. The cell-material contact may be direct; the cells grow next to, or even on the test material. In in vitro tests, direct cell/material contact methods simulate the in vivo situation in certain instances. In indirect contact, materials and cells are separated by a barrier. Eluates derived from a dental material by storing it for a specific period of time in a liquid, such as the nutrient medium, may be used for toxicity testing instead of the material itself. Besides the description of cell morphology, different biological endpoints can be used as indicators for cell damage: membrane effects, cell activity and proliferation rate. The cell reaction can be described morphologically as is done with the lysis index in the agar overlay test. However, this method is considered to be only qualitative, or at most, semi-quantitative in nature. Furthermore, some dental filling materials contain or produce considerable amounts of ingredients, which if applied to cells in culture; the morphology of the cells will appear to be normal, indicating no cell damage even though the cells are no longer vital (Schmalz & Netuschil, 1985). The use of membrane effects, cell activity and proliferation rate have no such drawbacks. Membrane effects can be demonstrated by dye exclusion (trypan blue). The trypan blue exclusion assay can be used to indicate cytotoxicity, where the dead cells take up the blue stain of trypan blue, and the live cells have yellow nuclei. Direct cell counting is easy to perform and can be combined with a vital stain in order to exclude dead cells.

8.2 Local toxicity related to ceramics

Different researches have been performed to study local cytotoxicity of dental ceramics. Cobb et al. (1988) investigated the in vitro biocompatibility of porous air-fired opaque porcelain with human gingival fibroblasts. Their results indicated that porous air-fired opaque porcelain is biocompatible. Then, Josset et al. (1999) studied the reaction of human osteoblasts cultured with zirconia and alumina by investigating cellular functions, and found that no cytotoxic effect was observed because neither material altered cell growth rate in accordance with the absence of any inducing effect on DNA synthesis or proliferation. Also, Sjögren et al. (2000) evaluated the cytotoxicity of different types of feldspathic porcelain ceramics by using cells from a mouse fibroblast cell line and the agar overlay test, Millipore filter test, and MTT (3-(4, 5-dimethylthiazol-2-y1)2, 5-diphenyl tetrazolium bromide)-based calorimetric assay. All the ceramics studied were rated “non-cytotoxic”. Consistent with the former study, Uo et al. (2003) tested the cytotoxicity of different feldspathic, leucite-reinforced glass, and lithium-containing ceramics against human gingival fibroblasts that were cultured using extraction solutions of ceramics, with the aid of almar blue assay. They found that no ceramic extractions showed any evidence of significant cytotoxicity.

Different implantation studies have been also performed for different types of ceramics in different tissues. Silicon oxide ceramic did not cause inflammation after implantation in muscle (G. Schmalz & C. Schmalz, 1981). Bioglasses based on silicon oxide were osteoconductive and osteoinductive when implanted in bone (Chan et al., 2002). Aluminum

oxide ceramic, before and after infiltration with lanthanum glass, was found to cause a significantly thicker connective tissue encapsulation and an increased number of inflammatory cells 12 weeks after subcutaneous implantation, compared with Teflon and titanium (Limberger & Lenz, 1991). On the other hand, aluminum oxide ceramic resulted in osseointegration in other studies and thus revealed a good compatibility with surrounding bone (Piatelli et al., 1996). There are obviously differences between the compatibility of various ceramics, and these may be correlated to different indications and applications and different contact with tissue (for example, core ceramic versus implant ceramics). Zirconium oxide ceramic showed good osseointegration when implanted in guinea pigs (Aldini et al., 2002). Calcium phosphate ceramics have been implanted in various animal models. Results were heterogeneous according to the materials tested and depended mainly on the following parameters: calcium (Ca)/phosphate (P) ratio, chemical purity, removal of organic compounds from raw materials, sintering technique, crystal structure (monophase or polyphase), and size and type of pores. Numerous macrophages and foreign body giant cells were observed histologically during the first weeks after implantation of absorbable TCP ceramics. The integration of non-soluble hydroxyl-apatite ceramic in bone without any cellular interface (osseointegration) indicates good biocompatibility (Lacefield, 1999).

Various degrees of ceramic toxicity have been stated. Messer et al. (2003) studied the cytotoxicity of feldspathic porcelains, lithium-disilicate ceramics, and leucite-based glass ceramics by testing their ability to alter cellular mitochondrial dehydrogenase activity (SDH activity) using tetrazolium assay. Their results revealed that dental ceramics are not equivalent in their in vitro biologic effect, even with the same class of material and most ceramics caused only mild in vitro suppression of cell function to levels that would be acceptable on the basis of standards used to evaluate alloys and composites (< 25% suppression of SDH activity). However, the lithium-containing ceramics exhibited cytotoxicity that would not be deemed biologically acceptable on the basis of prevailing empirical standards for dental alloys. Additionally, Pera et al. (2005) investigated the in vitro cytotoxicity of different ceramic materials (lithium-containing, aluminous, zirconium, and feldspathic ceramics) with the use of MTT testing on mouse fibroblasts. Their results revealed that not all tested materials were free from cytotoxicity. Other confirmatory studies have been reported by Elias et al. (2002); Yamamoto et al. (2004) who revealed a varying ability to induce inhibition of cell proliferation, cytotoxicity (as measured by colony forming efficiency) of silica, and alumina components in ceramic materials used for orthopedic prostheses.

It has to be noted that the biocompatibility has been mainly studied for traditional feldspathic porcelains. Most newer ceramic materials, such as those for computer aided design – computer aided manufacture (CAD-CAM) all-ceramic systems, have not been tested for biologic response with the same scrutiny as has been applied to dental casting alloys or even traditional ceramics. In vitro studies have reported different mass loss and cytotoxicity of some newer formulations of all-ceramic materials. An in vitro study done by the author of the current chapter (Elshahawy et al., 2009a) investigated the ion release from CAD-CAM leucite-reinforced glass ceramic material into both sodium chloride and lactic acid immersing solutions using inductively coupled plasma mass spectroscopy and showed that transient exposure of tested material to an acidic environment for one week is likely to significantly increase elemental release from it (e.g. aluminum and potassium ions). However, the amounts of these released elements (ions) were shown by the author of the

current chapter to be not enough to show high evidence of toxicity against cultured fibroblasts using the trypan blue assay (Elshahawy et al., 2009b).

Whatever is the dental material used for fixed prosthodontic appliance, it is nevertheless difficult to predict the clinical behavior of a material from in vitro studies, since oral factors such as changes in the quantity and quality of saliva, diet, oral hygiene, polishing of the material surface, amount and distribution of occlusal forces, or brushing with toothpaste, can all influence corrosion to varying degrees. From a biocompatibility standpoint, the corrosion of a material indicates that some of the elements are available to affect the tissues around it. Therefore, a study was performed by the author of the current chapter (Elshahawy et al., 2010) which quantitatively assess the element release from CAD-CAM fabricated leucite-reinforced glass ceramic crowns into saliva of fixed prosthodontic patients. They revealed the release of silicon and aluminum ions from them after three months in service. These released amounts were not enough to produce pronounced cytotoxic effects against fibroblasts.

9. Genotoxicity, mutagenicity, and carcinogenicity

9.1 Means of testing

The Ames assay is used worldwide as an initial screen to determine the mutagenic potential of new chemicals and drugs. It is perhaps the most rapid, simple, sensitive and economical screening test for mutagenicity and has an extensive database and good correlation with carcinogenicity.

The comet assay is a quick, simple, sensitive, reliable and fairly inexpensive genotoxicity test which is widely used to evaluate the genotoxic potential of chemical and physical substances. Ostling & Johanson (1984) first demonstrated "comets" and described the tails in terms of DNA with relaxed supercoiling through a process of electrophoresis (pH 9.5) of cells embedded and lysed in agarose on a microscope slide. Later, Singh et al. (1988) used alkaline electrophoresis to analyze DNA damage from treatments with X-rays or hydrogen peroxide (H_2O_2). Since then, the worldwide acceptance of Comet assay makes it a good assay for detecting DNA damage.

9.2 Genotoxicity, mutagenicity, and carcinogenicity related to ceramics

The mutagenicity (genotoxicity) of dental ceramics is not clear due to the lack of research focusing on this aspect. Takami et al. (1997) tested the mutagenicity of aluminous (Al_2O_3) ceramic by using Ames assay and tester Salmonella typhimurium strains TA98, TA100 and TA1535. Mutagenicity was not induced by extracted samples of the Al_2O_3 ceramic with and without metabolic activation in Salmonella typhimurium strains TA98 and TA1535. Another study by Covacci et al. (1999) in which zirconia ceramic stabilized by yttria (Y-TZP) was evaluated for mutagenic and carcinogenic potential in the form of discs did not show any mutagenic or oncogenic effects in vitro. A study by Noushad et al. (2009) found that dental ceramics did not induce any DNA damage after using tester Salmonella strains TA98 and TA1537 to detect frameshift mutations whereas using tester strains TA100 and TA1535 to detect base-pair substitution mutations. From previous studies, it is noted that some biomaterials are mutagenic to one tester strain while it is not mutagenic to another. Even though many investigators have sometimes used just 2 strains to determine the mutagenic

potential of biomaterials, it is felt that the use of at least four tester strains as recommended by Mortelmans & Zeiger (2000) gives a more definite result.

Other studies tested the mutagenicity and carcinogenicity of the different components of ceramics separately. For example, lithium is a component of certain ceramics. Leonard et al. (1995) reviewed the information available on the mutagenicity, carcinogenicity and teratogenicity of lithium. It was concluded that lithium is unlikely to be carcinogenic. Weiner et al. (1990) studied the effects of lithium hypochlorite in a series of tests including five strains of Salmonella. Lithium was not found to be genotoxic in any of the test systems with the exception of an equivocal response in the Chinese hamster ovary/hypoxanthine-guanine phosphor-ribosyl transferase assay, which was not replicable in a subsequent experiment.

Silica and alumina are main components of ceramics on which genotoxic studies have been reported. In one Comet assay, Zhong et al. (1997) indicated that silica and glass fibers can induce DNA damage in mammalian cells and that crystalline silica has a higher DNA-damaging activity than amorphous silica. Simon et al. (2007) assessed the genotoxicity of alumina and titanium oxide (TiO_2) using the Comet assay and showed that DNA damage was limited to single-strand breaks and/or alkali-labile sites and that genotoxicity was weak. From previous studies, the genotoxicity of some of the components of dental ceramics remains controversial.

Three decades ago, uranium salts were previously added at a concentration of 1,000 ppm to dental ceramics for simulating the natural luminescence of teeth. Because of the radioactivity of uranium salts, alternatives are now applied, such as oxides of rare earths. Today, radiation of dental ceramics is only due to natural radionuclides (mainly α and γ emitters) and much below the materials dated back to the times, when uranium salts had been added. Feldspathic ceramic specimens showed an activity concentration (Uranium/Thorium chains) that is in the same order of magnitude as for the human body. No radiation related adverse effects of dental ceramics have been documented in the literature (Veronese et al., 2006). Raw materials used for zirconium oxide ceramics (e.g., Zirkon, $ZrSiO_4$) may contain contaminants such as thorium and uranium. These contaminants generate α-, β-, and γ-radiation. However, the effective activity of zirconium oxide ceramic was far below the mean value of the annual exposure to natural radiation (Piconi & Macauro, 1999).

So far, no clinical reports have been published that document a carcinogenic effect of certain dental ceramic materials in the oral cavity. The long exposure time that is necessary for the emergence of a malignant tumor is a very aggravating factor for clinical assessment of potential carcinogenic properties. Therefore, it is only possible to draw indirect conclusions from other areas (e.g., occupational exposure to chemicals) to a possible carcinogenic effect.

10. Immunogenicity

As mentioned before, the term immunogenicity is referred to the ability of a substance to provoke an immune response or the degree to which it provokes a response. Sun et al. (2009) studied the clinical effects and security of nanometer ceramics artificial bone transplantation to treat the bone defect. After follow-up period for 24 months, the artificial bone has no immunogenicity, no rejection, does not affect the blood calcium and

phosphorus content, and has higher osteogenic activity. According to our knowledge, there is no documentation about sensitivity to ceramics.

Ceramics are rigid materials and therefore generally need to be luted to human hard tissues like teeth. There can be allergies/sensitivities to the cements/bonding agents that are necessary for the attachment of ceramic fixed prosthodontic restorations. Postoperative sensitivities have been observed in a few cases after the (adhesive) luting of ceramics (inlays, crowns) (Pallesen & Dijken, 2000; Studer et al., 1996). Also, one thing that may be an issue is that if the ceramic fixed prosthodontic restoration is impinging on a vital tissue, e.g. if margins of dental ceramic veneers are impinging on what is called the biologic width of gingiva (the amount of space under the gum where nothing can be placed) then a chronic state of inflammation will ensue.

11. Conclusion

1. Substances are released from ceramics into the surrounding tissues; mainly silicon, aluminum, potassium.
2. Systemic toxicity of ceramics is unlikely to occur due to the relatively low amounts of released elements such as lithium and lead.
3. Few ceramics have shown to be cytotoxic in vitro. The clinical relevance of these findings remains unclear.
4. Generally, local toxicity of ceramics is considered as low. However, more cytotoxicity researches are needed due to possible exceptions.
5. Overall, there is no evidence that ceramics cause or contribute to neoplasia in the body.
6. Ceramics are generally considered as biocompatible materials, although relatively little data are available.
7. Future biocompatibility studies should be performed to study more measurements dealing with cells functions such as protein fabrication (e.g. collagen synthesis), respiratory and digestive cell functions in a response to elements released from ceramics.
8. Future biocompatibility studies should be also performed to test the combinations of the elemental salts released from ceramic materials for the detection of synergistic, antagonistic, or additive effects caused by different mixtures of cations.

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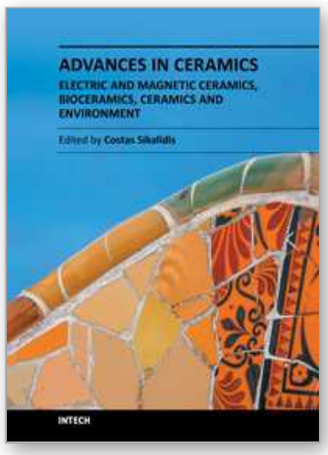

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