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Cytotoxicity of Dental Ceramics Used for Manufacturing Dental Fixed Prosthesis: A Systematic Review

Waleed Elshahawy[1]

[1]Department of Fixed Prosthodontics, Faculty of Dentistry, Tanta University, Tanta, 31111, Egypt.

Corresponding Author: Waleed Elshahawy, Department of Fixed Prosthodontics, Faculty of Dentistry, Tanta University, Tanta, 31111, Egypt, **Tel:** 2-0106-8754599; **Email:** dr_waleedelshahawy@yahoo.com

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ABSTRACT

Objectives: The common criterion for ceramic fixed prostheses is their permanent existence in the oral cavity for prolonged time without the ability to be removed by the patient. The purpose of this study was to systematically review the published literature on the cytotoxicity of dental ceramics.

Methods: MEDLINE via PubMed, Google Scholar, and Scopus databases for the period January 1985 to December 2014 were searched with the following key words: (biocompatibility OR cytotoxicity OR cell culture techniques) AND (dental ceramics OR dental porcelain OR ceramic fixed prosthesis). The inclusion criteria included in vitro studies using either animal or human cells, in which the cytotoxicity of the dental ceramics was tested. Studies that evaluated other parameters such as genotoxicity, mutagenicity and carcinogenicity were excluded. Articles published in the English language and in peer-reviewed journals focusing on the cytotoxicity of these materials were reviewed.

Results: Available data revealed that substances are released from ceramics into the surrounding tissues; mainly silicon, aluminum, potassium. Few ceramics have shown to be cytotoxic in vitro. The clinical relevance of these findings remains unclear.

Conclusion: Few ceramics have shown to be cytotoxic in vitro, however generally speaking; cytotoxicity of dental ceramics used for manufacturing fixed prosthesis is considered as low with defining ceramics as biocompatible materials. Further in vitro studies, as well as controlled clinical trials, are needed due to possible exceptions. Some bioceramics such as zirconia were proven to be a biomaterial of choice and also osteoconductive material that facilitate bone formation.

KEYWORDS

Ceramics; Cytotoxicity; Patients; Ion release; Biohazards.

INTRODUCTION

The use of dental restorations manufactured using ceramics has widely increased. Physical properties of these materials have improved to the point where they can be used in clinical situations, such as posterior crowns and fixed partial dentures.

Ceramics are usually defined in terms of what they are not: non-metallic (not metals) and inorganic (not resins). To distinguish them from rocks and minerals, the vast majority of which are also inorganic and non-metallic, ceramics are additionally define as man-made solid objects formed by baking raw materials (minerals) at high temperatures [1].

Biocompatibility and Cytotoxicity

The term biocompatibility refers to 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 [2]. Toxicity of a material describes the ability to damage a biological system by chemical means. Cytotoxicity refers to damage to individual cells, for example in cell cultures. Cells can die because of necrosis or apoptosis (programmed cell death). Therefore, cytotoxicity is an important component of biocompatibility.

Significance to Study Cytotoxicity of Dental Ceramics

Dental ceramics have seen wide scale use as restorative materials in dentistry. They are mainly used for manufacturing dental fixed prosthesis. The biocompatibility of fixed prosthodontic materials is a critical issue because these materials are in intimate contact with oral tissues for long terms and can not be removed by the patient [3]. Because of this nature of prosthodontic therapies, dentists therefore should depend heavily on dental biomaterials. This makes biocompatibility issues especially relevant to prosthodontists and other restorative dentists.

One common misperception of fixed prosthodontic materials is that it may be inert in the oral environment. The placement of a material into the oral cavity creates active interfaces through which the body affects the material and the material affects the body. Regardless of the material placed, these interactions occur depending on the material, the host, and the forces and conditions placed on the material (its function) [4]. Thus, the inertness of fixed prosthodontic materials, such as dental ceramics is not realistic and it is unlikely that ceramics will release nothing into the body.

Also, it has to be stressed that biocompatibility of fixed prosthodontic ceramics is often overlooked because many practitioners assume that, if a material is available in the market, its biocompatibility does not need to be questioned. Two systems are currently responsible for standards that can be used to document products quality: ANSI/ADA and ISO. They do not require specific biologic tests to approve the quality of a new dental material. Instead, 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 tests), and usage 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 [5]. Therefore, companies market materials with little clinical experience, and may rely heavily on in vitro and animal tests.

Cytotoxicity of Dental Ceramics

Generally speaking, one important condition that limits the relevance of in vitro cytotoxicity tests is the duration of the exposure of the tested material to the cell cultures. Most "direct contact" in vitro tests, which place the material directly adjacent to cells, are less than 168 hours long because of the various limitations involved in culturing cells for longer periods of time. These limitations include microbial contamination, loss of potency or nutrition of the medium, or cell overgrowth. The relatively short contact times are not relevant to materials such as dental ceramics, which are present in the mouth for years [6].

One alternative to direct contact testing is indirect contact testing. In this strategy, the tested material is cultured with cell culture medium (but no cells) for a specific length of time, and then the medium is transferred to the cells for toxicity testing in a second step. Using the indirect strategy, it is possible to "age" the material in a biological medium and change the extracted medium several times, testing its toxicity on cell cultures periodically. This strategy has been used to test the cytotoxicity of a variety of dental alloys. However, the indirect contact strategy had some disadvantages. The medium must be changed on the cells. This procedure can itself kill a percentage of the cells. Furthermore, the indirect system was not a dynamic system that allowed the material and cells to interact over time [7].

A second alternative to traditional direct contact testing is to first condition the material in a biological medium, then use a direct contact test to evaluate the cytotoxicity of the material, not the conditioning medium. This modified direct test allows the material and cells to dynamically interact, limits the practical problems of the indirect tests, and allows the material to be aged to give more relevant information [6].

As ceramic restorations are often in close proximity to periodontal tissues for extended periods, the biocompatibility of these materials is critical to their long-term safety. Different researches have been performed to study cytotoxicity of dental ceramics. The current article presents a literature review on these cytotoxicity researches discussed in a chronological order.

Earlier, Cobb et al. [8] 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 with human gingival fibroblasts. Various degrees of ceramic toxicity have been stated by Hyakuna et al. [9] who cultured V79 cells in direct contact with different types of hydroxyapatite ceramics (sintered at 600, 900, and 1200˚C), glass-ceramics, tricalcium phosphate and alumina-ceramics. Their results showed no toxicity for alumina, some toxicity for tricalcium phosphate, hydroxyapatite ceramics (1200°C) and glass ceramics, while hydroxyapa-

tite (600 and 900˚C) was highly toxic.

In addition, the cell reaction to powders of ceramics (zirconia, alumina, tricalcium phosphate and hydroxyapatite) was studied in vitro at various concentrations against cultured human fibroblasts. Alumina and hydroxyapatite showed no cytotoxic effects at studied doses (1-500 ug/ml) while zirconia and tricalcium phosphate inhibited cell viability, with 50% of the colony forming efficiency reduced at the concentration of about 50ug/ml. Also, sintered zirconia ceramic powder (obtained by crushing the sintered ceramic material) result in the same cellular response as with the zirconia powder [10]. Then, Josset et al. [11] 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, Sjogren et al. [12] evaluated the cytotoxicity of different types of ceramics (Vita VMK 95, Vitadur alpha, Empress Dentin, Duceratin T, and Duceratin D) by using cells from a mouse fibroblast cell line and the agar overlay test, Millipore filter test, and MTT test. All the ceramics studied were rated "non-cytotoxic". Consistent with the former study, Uo et al. [13] tested the cytotoxicity of different pressable (Empress-1 and Empress-2), machinable (Denzir), veneering (Vita VMK 68 and 95), conventional (Vitadur alpha and Vitadur N), and low-fusing veneering ceramic (Duceratin T and Duceratin D) 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.

On the other hand, Messer et al. [14] studied the cytotoxicity of feldspathic veneer porcelains (Vita Omega and Ducera-gold), two lithium disilicate pressable porcelains (Empress-2 and Stylepress), and a pressable leucite-based porcelain (Empress-1) by testing their ability to alter cellular mitochondrial dehydrogenase 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 biologic safety should not be assumed. 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, Empress-2 exhibited cytotoxicity that would not be deemed biologically acceptable on the basis of prevailing empirical standards for dental alloys. Additionally, Pera et al. [15] investigated the in vitro cytotoxicity of five ceramic materials (In-Ceram, Cergo, IPS Empress-2, Cercon ZrO2, and Finesse) 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. [16]; Yamamoto et al. [17] 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.

Therefore, the proper biocompatibility of dental ceramics has been largely assumed based on studies of traditional feldspathic porcelains and the low corrosion rates of feldspathic material. 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 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) [18]. However, the amounts of these released elements (ions) were not enough to show high evidence of toxicity against cultured fibroblasts using the trypan blue assay [19].

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 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 [20, 21].

Regarding zirconium ceramics, in vitro tests [22-25] were made to test its biocompatibility. Samples of zirconium were tested on fibroblast, lymphocyte, macrophage, monocyte and osteoblast. On osteoblast, zirconia did not induce any pseudoteratogenic effects (DNA quantity of cells). On fibroblast, zirconia

could somehow cause toxicity. However, it is also worthwhile to note that this in vitro data obtained could be partly dubious because of the material characteristics (e.g. reactive surface, impurity content and chemical composition). On macrophage and monocyte, powders and particals of zirconia did not induce high cytotoxicity or inflammation [22]. Another research found that the most frequent early complications of zirconia were localized gingival irritation and postoperative tooth sensitivity [23].

Many studies however stated that zirconia is a biomaterial of choice and also osteoconductive material that facilitate bone formation when it is used in implantology. Cho et al. [24] tested the osteogenic response of zirconia with hydroxyapatite (HA) coating by aerosol deposition. This in vitro study was made using surface analysis by scanning electro-microscope and X-ray diffraction. The result showed that surface of HA-coated zirconia exhibited a less osteoblastic proliferation than those on uncoated zirconia, and bone marker gene expression analysis indicated good osteogenic response on HA-coated Zirconia. In accordance, Chen et al. [25] found that incubation of human osteoblast with zirconia ions increased the proliferation of human osteoblast and also gene expression of genetic markers of osteoblast.

CONCLUSIONS

Few ceramics have shown to be cytotoxic in vitro, however generally speaking; cytotoxicity of dental ceramics used for manufacturing fixed prosthesis is considered as low with defining ceramics as biocompatible materials. Further in vitro studies, as well as controlled clinical trials, are needed due to possible exceptions. Some bioceramics such as zirconia were proven to be a biomaterial of choice and also osteoconductive material that facilitate bone formation.

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