JOURNAL OF COMPLEMENTARY MEDICINE RESEARCH

RESEARCH ARTICLE

Cellular Toxicity of Dental Restorative Materials on The Gingival Fibroblasts

MORTEZA SHARIFI [1], REZA KHODADADI [2]*, MOHAMMAD TAVAKOLI [3], MASOUMEH BEHDARVANDI [4]

[1]*DDS, MSc, Assistant Professor of Prosthodontics, Department of Prosthodontics, School of Dentistry, Isfahan University of Medical Sciences, Isfahan, Iran*

[2]*Assistant Professor of Prosthodontics, Department of Prosthodontics, School of Dentistry, Dental Implants Research Center, Isfahan University of Medical Sciences, Email: Khodadadi@dnt.mui.ac.ir*

[3]*Department of Periodontology. Dental Implants Research Center, Dental Research Institute, School of Dentistry, Isfahan University of Medical Sciences, Isfahan, Iran*

[4]*Post Graduate student, Dental Student Research Committee, Department of Endodontics, School of Dentistry, Isfahan University of Medical Science, Isfahan, Iran*

**Corresponding Author*

ABSTRACT

Dental restorative materials (DRMs) have a vast market worldwide. Today, investigators are working on the new DRMs with well aesthetic properties, optical durability, well biocompatibility, and less toxicity. Anyhow, DRMs contain ingredients that release them into the interstitial gingival space and even the bloodstream. Hence, the DRMs ingredients toxicity is a concern in odontology.

Researchers use the cell line models to explore DRMs toxicity in the in vitro environment. The human gingival fibroblasts (hGFs) have been known for their use in basic odontology sciences for many years. Novel DRMs should be tested for their toxicity on the hGFs before evaluation in clinical trials. In this narrative review, we have presented various aspects of the DRMs toxicity for the hGFs. This review emphasizes that DRMs harbor low cytotoxic effects on the hGFs during a short-term period. DRMs cytotoxicity depends on the type of restorative composite and its ingredients concentration, the release of prostheses particles/ions into the hGFs environment. Other determinative factors for cytotoxicity potency of DRMs include the composite chemistry, its degradability, mechanical properties, and surface topography. Nonetheless, animal experiments and clinical trials should confirm the data from hGFs studies.

KEYWORDS:
Dental Prosthesis, Cell Line, Biocompatible Materials, Dental Restoration Wear.

ARTICLE HISTORY:
Received Oct 14, 2021
Accepted Nov 22,2021
Published Dec 22, 2021

DOI:
10.5455/ jcmr.2021.12.04.25

VOLUME: 12
ISSUE: 4
ISSN: 2146-8397

INTRODUCTION

Dental restorative materials (DRMs) have a global market volume of around ten billion dollars. A market volume evaluating team expected $10.5 billion by 2020 for dental implants and prosthetics. New replacements for amalgam and resin-based restoratives are expected to enter the market in the following years (1). DRMs market is growing in those countries with population aging. Dentistry services have a burden in developing countries. The need for implants or prostheses will be growth subsequently. The good examples for this matter are middle east countries. The good examples for this matter are middle east countries.

Computer-aided design (CAD) and computer-aided manufacturing (CAM) are extensively applicable in odontology and related researches. These facilities opened new insight into DRMs usage (2). Modern technology usage such as 3D printing, CAD/CAM processors, tissue engineering, and molecular toxicology study outcomes determine which material could be a restorative agent (1). Classically, certain DRMs have been shown to interact with living tissues via chemical bonds and become biocompatible and tolerable with the implant location. Ion leaching, dissolution, and precipitation are mechanisms by which restorative glasses bond to the living tissues (3).

After implantation, depending on the type of used material, ingredients of the prosthesis could react with the surrounding tissue. Inflammatory responses will occur, and inflammatory cytokines release at the site of implantation, its periphery, and the general circulation (4). A research team showed that colloidal silver nanoparticles used in endodontic treatments are toxic for the L929 cell line, a type of mouse fibroblast in higher than 25 µg/mL concentrations, in vitro. Silver nanoparticles did not significantly induce interleukin-1ß production, but they did provoke the L929 cell line to release the stem cell factor after 48 hours of treatment with 5 µg/mL concentrations (5). These examples indicate that DRMs interact directly with the gingival tissue when their ingredients release into the interstitial environment. Cytotoxicity occurs after DRMs ingredient release and according to the type and concentration of each chemical agent of composite. Today, DRMs manufacturers attempt to develop glass-ceramics materials instead of metals and ceramics composites to overcome their imperfections. Examples of new glass-ceramics proposed by investigators include fluorrichterite, fluorcanasite, diopside, and apatite-mullite glass-ceramics (1).

Importance of this review

Ceramics have been used throughout mankind's history. But, in 1972, a crystalline sapphire aluminum oxide implant was used as a tooth that adsorbed the attention due to its aesthetic properties than the metal implants. It has excellent tissue biocompatibility, although with problems during and after implantation. Fractured implant, mobility, infection and inflammation, bone damage, and low osseointegration were the most frequent outcomes (6). Today, novel and excellent replacements are known and used as the prosthetics, such as bioactive ceramics, metals, and alloys. But the field of implantology research is open, and investigators are working on new replacements of DRMs with better function, physical properties, aesthetic characteristics, biocompatibility with lower cytotoxicity. In this regard, we suppose to review the biocompatibility and cytotoxicity of vastly used DRMs. We hope this review to be informative for investigators in the field of odontology and implantology.

METHOD OF REVIEW

We have reviewed PubMed, google scholar, and ScienceDirect for the most related investigations on the toxic effect of dental prosthesis materials on human gingival fibroblasts (hGFs). We do searches without any time limitation for publications. Search language was English, any article type, including original and reviews, was used in this report. We do not include anything in this narrative review. After evaluating each article abstract, for their relationship with the hGFs toxicity of DRMs, we made screening on the reports to review them extensively.

Systems to evaluate dental material toxicity

There are various in vitro, ex-vivo (cell culture), animal experiments, and clinical methods to determine the toxicity of the DRMs. Overall, from these methods, the cell cultures are extensively used DRMs toxicity screening. The hGFs have been used frequently in DRMs toxicity determination, biocompatibility, and safety evaluations (7). Therefore, this type of cell line has a central role in the DRMs surveys. Although there are several studies on the DRMs using the hGFs model, the limitation of the results of cell lines should not be missed (7). The results obtained from cell line studies need to be confirmed by experimental and clinical investigations.

Human gingival fibroblast cell

Human gingival fibroblasts, the hGFs, are used as a cell line model in regenerative medicine. The hGFs resemble mesenchymal stem cells for their similar morphology, CD markers, and differentiation lineage. These cell lines are characterized by positive fibroblasts Antibody (TE-7) and negative Pan-Cytokeratin. This cell line is separated from adult gingival tissue and is adherent-dependent and fibroblast-like cells. For their proliferation, the hGFs need growth factors, fibroblasts basal medium, fetal bovine serum, humidified 37°C incubators with 5-10% CO2 (8). Odontology scientists have published several reports about the physical, chemical, and biological properties of DRMs tested on the hGFs different culture systems (2). Briefly, we have reviewed the most important aspects of the DRMs property affecting the hGFs behavior in the culture medium based on the scientific essays.

Mechanical and chemical degradation of dental ceramics

The complications of dental ceramics include their tendency to abrade dental strictures, roughening their surface after interaction with chemicals, and plaque formation. In addition, the toxic element release, due to the dissolution and radioactive emission arising from their composition materials, is the other concern. Dental ceramics degradation is due to mechanical forces or chemical attacks (9). Both acidic and basic environments are proposed to degrade the glass-ceramic veneers and overglazes. Investigators have tested the glass-ceramic veneer and glaze in acidic, neutral, and alkaline buffer solutions for 1, 3, 5, 10, and 30 days in an 80°C water bath. They have reported that the Si4+ is released at pH 10, which leads to the breakdown of the glass phase. Other studied ions, i.e., Al3+, Ca2+, Zn2+, and Li2+ exchanged during the treatment period. These findings are representative of the fact that the ceramic veneers and glazes are degradable at the acidic and alkaline solutions (10). Li and coworkers also showed that zirconia ceramic plate and yttrium slowly release ions in saline or 0·02 M lactic acid (pH 2·72) solutions (11).

CAD/CAM materials help dentists to do restorative interventions. CAD/CAM materials exhibit different chemical

and mechanical properties depending on their type. In an experiment for CAD/CAM materials, including 3M ESPE LAVA Ultimate, VITA Enamic, IPS e.max CAD, and VITA Suprinity have been conditioned at 37°C for seven days in the presence of artificial saliva, alcohol, citric acid, lactic acid, and aqueous solution to test the flexural strength, hardness, and wear characteristics. Tested materials had different mechanical properties when conditioned in the chewing simulator. The e.max and VITA Suprinity, harbor the best results and the worst outcomes were for LAVA Ultimate. The mechanical properties of e.max CAD and Suprinity were negatively affected in acidic status whereas, the LAVA Ultimate and Enamic were affected by ethanol and heptane meaningfully (12). These results show the direct impact of strength and chemical status on the quality changes of CAD/CAM materials.

In another effort, the ceramic and resin materials composed of high-strength zirconium dioxide, machinable lithium disilicate, pressable lithium disilicate ceramic, fluorapatite-based glass-ceramic, and the color-graded feldspathic porcelain were stored in distilled water at 37°C for 14 days. Initial strength (σin) in 4-point bending was loaded on the specimens, and the residual flexural fatigue strength (σff) was measured for 104 cycles at 0.5 Hz. From tested materials, resin composites had better results than others. Therefore, researchers proposed resin composites as the alternative to glass-rich-ceramics inlays considering mechanical characteristics (13). This evidence implies that the degradation of dental ceramics is dependent on the material composition. Hence, dental ceramics could be the source of toxic or sensitizing agents released in the gum and the oral cavity, in addition to the entrance to the bloodstream. Cytotoxic elements in dental ceramics may harbor complications in the short term, i.e., inflammation or long-term toxicity. Long-term toxicity may be without considerable side effects, and detection of the complication source is not simply achievable or demonstrable in routine clinical evaluations.

Mechanical properties of dental ceramics

The dental ceramic type and adhesive cement both are determinative for safety and strength bonding properties to have a functional dental implant. However, the fixed prosthesis should prepare good elasticity and resistance without or lesser release of alloy components in the oral cavity and periodontal tissue (14). Mechanical properties of dental ceramics are determined by strength testing, fracture toughness, and roughness. Boron nitride nanoplatelets have been introduced as a dental material with good biocompatibility and enhanced mechanical properties (15).

Biocompatibility of DRMs

Biocompatibility is the ability of a safe material to work appropriately without stimulating host response. Therefore, a material could be unfamiliar with the body yet tolerable and without adverse reaction. DRMs may contain toxic materials, evoke inflammatory and immune system responses, and release cytotoxic ions and elements (7). Ceramic-based prosthetic materials are used commonly for dental restoration because of their chemical and optical durability, aesthetic, and biocompatibility characteristics, in addition to inert restorative material. Nonetheless, their abrasive effect on the natural teeth, occlusal interactions, and abnormal wear is the concern of their application (16, 17). Most studies on the quality of dental ceramics have been done using mechanical and chemical simulators. In an ex-vivo study, the hGFs were exposed to the lithium disilicate, zirconia dioxide, or titanium with two different surface roughnesses (0.2 μm and 0.07 μm). After assessment of cell proliferation, cell viability, cytotoxicity, and inflammation markers or signals on the day 1 and 21 of treatment, there were no differences between groups for roughness. Zirconia dioxide had a higher cytotoxic effect, whereas lithium disilicate showed a slight impact on the treated cells for the tumor necrosis factor-alpha (TNF-alpha) production, compared to zirconia dioxide or titanium. The results of the mentioned study emphasized that both dental ceramic formulations were suitable for specific clinical dental applications due to the low toxic effects (4). Gali and coworkers have shown the extensive growth of the hGFs in culture media with proper cell-to-cell bridge occur after exposure to the zirconia reinforced mica glass-ceramic (18). Grenade and colleagues have tested a polymer-infiltrated-ceramic-network (PICN) material compatibility with hGFs proliferation, attachment, and spreading properties. In addition, they compared PICN with titanium (Ti), yttrium zirconia (Zi), lithium disilicate glass-ceramic (eM), and control material the polytetrafluoroethylene. They have reported that Ti and Zi had better results regarding hGFs proliferation. However, PICN and eM had intermediate effects for hGFs growths properties. Ultimately, this research team suggested clinical trials for clarifying the PICN utilization as a bone prosthesis or implant (19). In another study, researchers have not seen any cytotoxic effect of nanocrystalline diamond coating on a mouse cell line and hGFs. Even slight proliferation enhancement was evident (20). Such evidence confirms that DRMs are interactive at the implantation site; however, they are slow reactants, and hence short-term adverse effects after implantation may not be expected. Nevertheless, we think long-term complications are probable for a regenerative process and are dependent on the hGFs tissue reserve.

Although zirconia polycrystal ceramics have excellent mechanical properties and biocompatibility, yet manipulation of its surface is difficult for enhancing its durability and strength of chemical bonds. Nevertheless, investigators have proposed approaches to improve the quality of zirconia ceramics surface bonding (21). In an effort, Vita Enamic®, a polymer infiltrated ceramic (PIC), was compared with Zirconia, Leucite, and Zirconia Veneered, when tested against natural teeth. After 360,000 cycles with 49N load in a chewing simulator containing artificial saliva, the teeth wear was evaluated by scanning electron microscopy. The best restorative ceramic material was Zirconia because of its lower occlusal interaction. The Vita Enamic®led to the

highest wear, whereas Leucite and Zirconia Veneered had the highest cusps' wear (16). Another study reported that the surface roughness of Noritake®& IPS Emax ceram, two dental ceramics, were increased after exposure to a Coca-Cola, a chlorhexidine mouthwash, and simulated vomit solution than distilled water (17).

Among the dental ceramics, the most interested DRMs include zirconia, glass, and polymer-infiltrated ceramics that are all biocompatible. Bioactive glass-ceramics are inert, biocompatible, and enable to make bone-binding interactions without adverse effects on the tissue interface (1). Investigators have been shown that the biocompatibility of dental ceramics may be enhanced using specific treatments. For example, the treatment of zirconia ceramic with oxygen plasma treatment is shown to increase its hydrophilicity. Such treatment also was beneficial for the cell growth of human osteoblast-like cells (MG63) (22). However, for biocompatibility tests, traditional methods include in vitro tests using cell culture and chemical simulators using artificial saliva, in vivo models using animal experiments, and clinical trials (14).

Cytotoxicity and safety of DRMs

The main issue of biocompatibility of dental prostheses is cytotoxicity because of intimate and long-term contact with oral tissue (14). The hGFs cell-line model and ovo chick chorioallantoic membrane (CAM) assay are used for cytotoxicity evaluation of dental ceramics in terms of in vitro models. Researchers have exposed hGFs to three types of dental ceramics included lithium disilicate, zirconia dioxide, and titanium. Treated hGFs were evaluated for proliferation, living/dead cell counts, cytotoxic and inflammation markers, in addition to the cell morphology by electron microscopy. This study showed a slight difference between tested materials; however, zirconia dioxide had higher cytotoxic effects. One day exposure to the lithium disilicate resulted in the lower TNF-alpha gene expression by hGFs compared to zirconia dioxide- or titanium-treated cells. Nonetheless, after 21 days of exposure, there was an insignificant difference among treated groups (4).

Recently, investigators have shown that the application of ceramics structures on 3D scaffolding for dental bone substitution could be safe and usable for clinical studies. In an effort, researchers have developed two new dental ceramics by the foam replication method and compared their physicochemical characteristics and cytotoxicity with two Cerabone®, a bone argumentation traditional material. Comparable results were obtained for new and traditional materials considering biocompatibility tests using the hGFs cell line. Dental ceramics had no irritative impact on the vascular plexus. The authors suggested that the clinical application of tested ceramics should be determined (23). Dental ceramic extracts are shown to be safe and with no significant cytotoxic effect on the hGFs. Therefore, other properties of ceramic materials are under attention, such as bonding strength. For instance, in a study on eight commercial dental ceramics, glass ionomer ceramic had meaningfully higher bonding strength than zinc phosphate (24).

Nonetheless, cytotoxic effects are reported for two types of lithium disilicate ceramics. The cell viability is determined by the 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) method. This test works based on the mitochondrial succinate dehydrogenase activity. Brackett and colleagues have shown that hGFs exposed to the lithium disilicate ceramics showed a significantly decreased viability (50-70%; compared to Teflon control) in the first two weeks. For some tested materials, the mitochondrial toxicity was decreased by the next two weeks but relapsed 10-20% after 4-6 weeks of evaluation (25). The cytotoxic effect of dental ceramics alloys may not be equivalent, even within the same class of material. In a study, five dental ceramics, including two traditional feldspathic veneer porcelains, two lithium disilicate pressable materials, and one pressable leucite-based material, were tested. Assessment of mitochondrial dehydrogenase activity after aging for two weeks or after post-aging polishing models showed mild suppression of cell viability. In this study, all types of dental ceramics had acceptable biological toxicity expected for dental alloys except the Li-disilicate material (26).

Pandoleon and colleagues have compared the effect of yttria-stabilized zirconia (Y-TZP), lithium disilicate (LS2), and titanium alloy (Ti) on the hGFs behaviors. They have evaluated the hGFs with no treatment status, aging circumstances (134 °C, 2 bars, 100% humidity) for 5- and 10-hours. They explored also the viability and proliferation properties of hGFs under treatment with these dental implant abutment materials. The results of this study showed that Y-TZP and LS2 reduced the cell viability of hGFs, meaningfully. Overall, Y-TZP and LS2 had a similar effect on hGFs, and all tested materials induced cell differentiation. However, Y-TZP aging influences the long-term maintenance of the gingival structure (27). Sabaliauskas et al. have examined the toxicity of titanium, dental gold alloy (composed of Au, Pt, and Zn), chrome-cobalt alloy (composed of Co, Cr, W, Nb, Mo, Si, Fe, C), and feldspathic ceramics. After 48 hours, titanium was not toxic for hGFs but gold alloy and feldspathic ceramic decreased cell viability, insignificantly. Chromium-cobalt alloy was toxic for hGFs compared to the control group long-time incubation (120 hours) was not accompanied by cell toxicity for all tested materials except for chromium-cobalt alloy (28).

Kurzmann and coworkers have evaluated the impact of two types of resins used in a 3D printing method on cell viability and toxicity of L929 and hGFs. The L929 cell line is used for toxicity testing and hGFs represent oral soft tissue. They stated that dental clear resin contains methacrylate oligomers, methacrylate monomers, and photoinitiators. These materials exert their oral and dermal toxicity in doses >2000 mg/kg, and >5000 mg/kg, respectively. Anyhow, Kurzmann and coworkers have tested the cytotoxicity of two types of dental resins containing methacrylate compounds, and photoinitiators. They have noted reduced cell activity

after treatment with tested resins. They have declared that printed and post-cured resins are not inert and exert their toxic impact in mono or oligomeric forms (2). Even, the culture materials or models, direct and indirect, of hGFs or L929 are not too determinative in the toxic effect exertion of the resins. The type of resin is the major factor for its cytotoxic behaviors (2, 29). The published studies suggest that methacrylate compounds exert their cytotoxic effects via induction of apoptosis, genotoxic effects, and the delay of the cell cycle (30, 31). The protective effects of antioxidants and cellular adaptation have been described as the protective mechanisms against methacrylate compounds. Accordingly, investigators have proposed that adverse effects of methacrylate compounds are related to the generation of reactive oxygen species (2, 31, 32). Overall, we propose a model for cytotoxic impact of DRMs, represented in Figure 1.

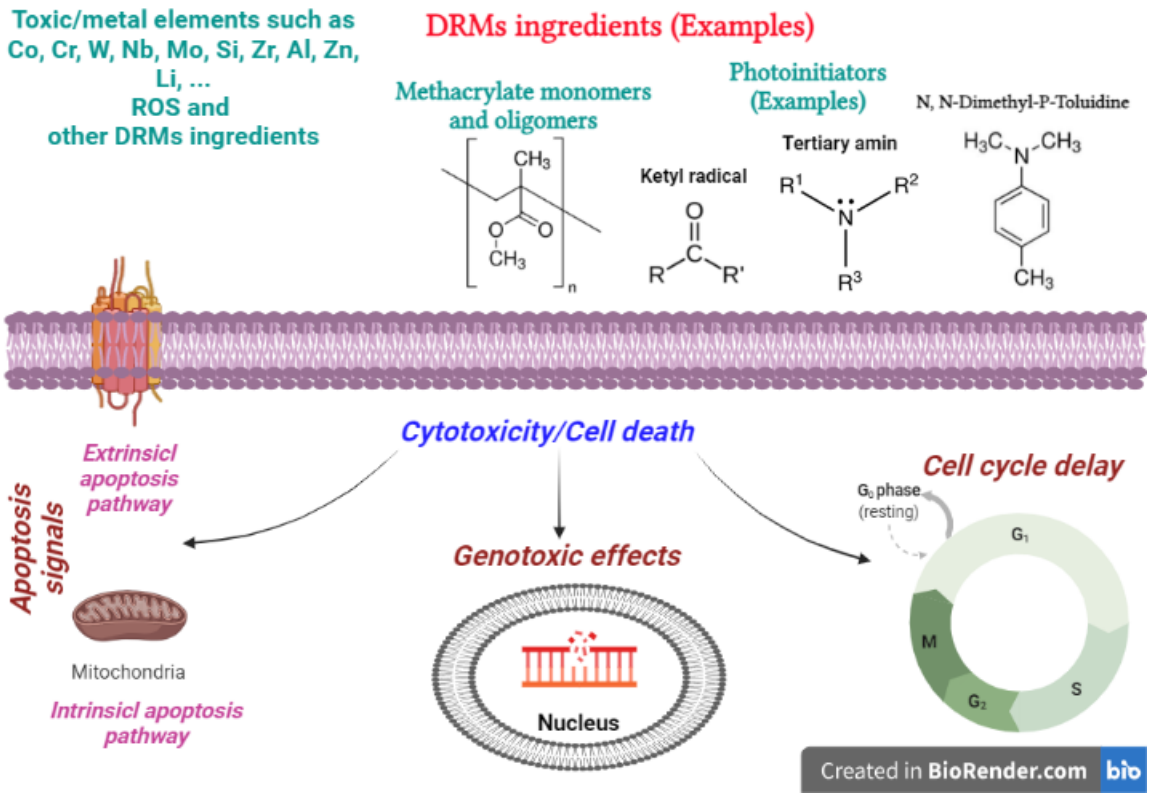

Fig.1: Proposed mechanisms of cytotoxicity induced by the dental restorative materials (DRMs). Toxic elements or metals, reactive oxygen species (ROS), photoinitiators, and other DRMs ingredients can promote cytotoxicity. After apoptosis activation, DNA damage, gene expression problems, and the cell cycle delay, cell viability decreases. We have drawn this image using BioRender online software.

Prostheses ingredients release into the peripheral tissue

Different elements used in dental alloys and composites may be released into the mouth cavity. The most frequently used glass-ceramics are manufactured from Leucite-based, Mica-based, lithium disilicate, zirconium dioxide (ZrO2)-reinforced lithium disilicate, apatite-based, and Sanidine (1). Toxic substances may be diffused and leached into the subgingival or systemic blood circulation. This leads to inflammation and adverse effects in surrounding oral tissues (28). Usually, at least four types of metals are used in each dental prosthesis alloy. More than 25 types of elements are applicable in dental alloys manufacturing (14). Hence, releasing each chemical element into the oral cavity or systemic blood circulation could be associated with long-term consequences.

Anyhow, researchers have shown that released elements exert no cytotoxic or moderately toxic impacts. The cytotoxic effect of alloys could be related to the related to the composite chemical elements, as is shown in experiments. In this regard, copper and zinc have been suggested to be the cause of toxicity to mouse fibroblast cell lines (33). The most investigated metal ions that are prone to release into the body from dental alloys composed of Nickle, Chromium, Silver, Palladium, Gold, Gallium, Beryllium, Molybdenum, Iron, Titanium and Lithium, each one may be in reduced or oxidized status. Corrosion of dental alloys can release each metal element/ion into the systemic circulation (14). Based on these findings, it is suggested the blood concentration of toxic elements used in dental composites to be evaluated in clinical studies. However, the quality of manufacturing dental alloy is important especially when heavy metals are used in the composites. Heavy metal entrance into the body is associated with serious complications during long-term exposure, renal insufficiency, and dialysis treatment (34, 35). The environment status could affect the teeth' enamel and probably the surface of implants and the release of its degradable components. It is shown that hydrogen peroxide bleaching for short intervals reduces the hardness of enamel and mineral content (36).

Along with dental ceramics that are used for dental implants, the filling materials may exert cytotoxic effects. In an effort

in 2017, researchers compared the toxicity of new resin-composite blocks (RCBs) with conventional materials (Filtek Z250 and Tetric EvoCeram). Compared to conventional materials, the RBCs were more toxic for hGFs and the epithelial cell line (37). Overall, the concentration of cytotoxic elements released in the bloodstream and gingival tissue should be evaluated using sensitive methods, especially where the measurement method needs no complicated process.

Surface topography

Pre-implant inflammation is dependent on the type of used implanted material, its composition, and surface topography. Modification of surface topography is used to improve dental ceramics characteristics including translucency and opalescence, tribological and biological properties affecting their osseointegration. Nowadays, laser surface texturing is under attention in dental implantation. Recently, researchers proposed the zirconia-based dental ceramics instead of titanium implants, but the existed challenges are the brittle nature of Zirconia-based ceramics and its metastable tetragonal ZrO2 phase (38). The surface roughness of a dental implant influences its interaction with the environment and clinical behavior. For example, roughness above 0.2 μm can result in plaque accumulation, periodontal inflammation, and increased risk of dental caries (39). The surface topology also has a role in the formation of microbial biofilms. The manufacturing techniques and finishing procedures are shown to be determinative in microbial colony formation, the type of dominant infective agent. In turn, the microbial colonization and their metabolites threaten hGFs viability (40).

Anyhow, the type of implanted material and polishing method affects the quality of the surface structure. The smoother surfaces of dental implants can be obtained using glazed lithium disilicate and zirconia-reinforced lithium silicate. Anyhow, glaze sprays and glaze paste application accompanied with rougher surfaces in other studies (39). The DRMs microtopography affects gingival tissue for fibronectin and collagen production (41). Hence prepares a suitable niche for the proliferation and expansion of hGFs. This process is helpful in faster implant site healing.

Petrini's research team has tested the response of hGFs to titanium implant discs having different micro and nano-topography. In addition, they have explored the effect of the macrogeometry of the manufactured Ti discs on the surfaces of the cells using atomic force microscopy (AFM) and scanning electron microscopy (SEM) analysis. They have shown that micro and nano-topography, manufactured with different technology, were not toxic for hGFs. The proliferation of hGFs was higher in Ti linear discs than wave-like surface discs (42). Proper surface topography of an implant is required for the correct mechanical function of the tooth. Degradation of the DRMs, due to unsuitable topography, induces the release of ingredients into the gastrointestinal tract or bloodstream. Nonetheless, all assumptions or theories need extensive studies on animal experiments or clinical trials.

CONCLUSION

DRMs are not seriously toxic for hGFs in a way immediately monitoring to be necessary for their physiological complications. Nevertheless, the long-term impact of dental prosthesis materials should be explored for their toxicity to other organs than gingival tissue and month. Toxic ingredients in dental alloys, such as trace elements/metals, could be associated with organ failure in the long term, such as renal damage. Therefore, we propose reports from phase-4 clinical studies based on the documentation from several dentistry clinics. Multicenter studies are required to clarify the long-term complications of DRMs on the hGFs.

REFERENCES

1. Montazerian M, Zanotto ED. Bioactive and inert dental glass-ceramics. J Biomed Mater Res A. 2017;105(2):619-39.
2. Kurzmann C, Janjić K, Shokoohi-Tabrizi H, Edelmayer M, Pensch M, Moritz A, et al. Evaluation of resins for stereolithographic 3D-printed surgical guides: the response of L929 cells and human gingival fibroblasts. BioMed research international. 2017;2017.
3. Moghanian A, Ghorbanoghli A, Kazem-Rostami M, Pazhouheshgar A, Salari E. An Introduction to Bioceramics. Structure. 2019.
4. Jung S, Moser MM, Kleinheinz J, Happe A. Biocompatibility of Lithium Disilicate and Zirconium Oxide Ceramics with Different Surface Topographies for Dental Implant Abutments. Int J Mol Sci. 2021;22(14).
5. Takamiya AS, Monteiro DR, Bernabé DG, Gorup LF, Camargo ER, Gomes-Filho JE, et al. In Vitro and In Vivo Toxicity Evaluation of Colloidal Silver Nanoparticles Used in Endodontic Treatments. Journal of Endodontics. 2016;42(6):953-60.
6. Haubenreich JE, Robinson FG, West KP, Frazer RQ. Did we push dental ceramics too far? A brief history of ceramic dental implants. J Long Term Eff Med Implants. 2005;15(6):617-28.
7. Polyzois GL. In vitro evaluation of dental materials. Clinical Materials. 1994;16(1):21-60.
8. ATCC. Primary Gingival Fibroblast; Normal, Human, Adult (HGF) 2021 [Available from: https://www.atcc.org/products/pcs-201-018.
9. Anusavice KJ. Degradability of dental ceramics. Adv Dent Res. 1992;6:82-9.
10. Esquivel-Upshaw J, Dieng F, Clark A, Neal D, Anusavice K. Surface degradation of dental ceramics as a function of environmental pH. Journal of dental research. 2013;92(5):467-71.
11. Li J, Liu Y, Hermansson L, Soremark R. Evaluation o biocompatibility of various ceramic powders with human fibroblasts in vitro. Clinical materials. 1993;12(4):197-201.
12. Sagsoz O, Polat Sagsoz N. Chemical degradation of dental CAD/CAM materials. Bio-medical materials and engineering. 2019;30(4):419-26.
13. Belli R, Geinzer E, Muschweck A, Petschelt A, Lohbauer U. Mechanical fatigue degradation of ceramics versus resin composites for dental restorations. Dent Mater. 2014;30(4):424-32.
14. Elshahawy W, Watanabe I. Biocompatibility of dental alloys used in dental fixed prosthodontics. Tanta Dental Journal. 2014;11(2):150-9.

15. Lee B, Kwon JS, Khalid MW, Kim KM, Kim J, Lim KM, et al. Boron nitride nanoplatelets as reinforcement material for dental ceramics. Dent Mater. 2020;36(6):744-54.
16. Santos F, Branco A, Polido M, Serro AP, Figueiredo-Pina CG. Comparative study of the wear of the pair human teeth/Vita Enamic(R) vs commonly used dental ceramics through chewing simulation. J Mech Behav Biomed Mater. 2018;88:251-60.
17. Zakir T, Dandekeri S, Suhaim KS, Shetty NHG, Ragher M, Shetty SK. Influence of Aerated Drink, Mouthwash, and Simulated Gastric Acid on the Surface Roughness of Dental Ceramics: A Comparative In Vitro Study. J Pharm Bioallied Sci. 2020;12(Suppl 1):S480-S7.
18. Gali S, Ravikumar K, Murthy B, Basu B. Zirconia toughened mica glass ceramics for dental restorations. Dental Materials. 2018;34(3):e36-e45.
19. Grenade C, De Pauw-Gillet M-C, Gailly P, Vanheusden A, Mainjot A. Biocompatibility of polymer-infiltrated-ceramic-network (PICN) materials with human gingival fibroblasts (HGFs). Dental materials. 2016;32(9):1152-64.
20. Amaral M, Gomes P, Lopes M, Santos J, Silva R, Fernandes M. Cytotoxicity evaluation of nanocrystalline diamond coatings by fibroblast cell cultures. Acta biomaterialia. 2009;5(2):755-63.
21. Xiang D, Lin H. Research progress in surface bonding pretreatment of dental zirconia ceramics. Zhonghua Kou Qiang Yi Xue Za Zhi. 2020;55(5):348-52.
22. Wu CC, Wei CK, Ho CC, Ding SJ. Enhanced Hydrophilicity and Biocompatibility of Dental Zirconia Ceramics by Oxygen Plasma Treatment. Materials (Basel). 2015;8(2):684-99.
23. Fabricky MMC, Gabor AG, Milutinovici RA, Watz CG, Avram S, Draghici G, et al. Scaffold-Type Structure Dental Ceramics with Different Compositions Evaluated through Physicochemical Characteristics and Biosecurity Profiles. Materials (Basel). 2021;14(9).
24. Uo M, Sjogren G, Sundh A, Watari F, Bergman M, Lerner U. Cytotoxicity and bonding property of dental ceramics. Dent Mater. 2003;19(6):487-92.
25. Brackett MG, Lockwood PE, Messer RL, Lewis JB, Bouillaguet S, Wataha JC. In vitro cytotoxic response to lithium disilicate dental ceramics. Dent Mater. 2008;24(4):450-6.
26. Messer RL, Lockwood PE, Wataha JC, Lewis JB, Norris S, Bouillaguet S. In vitro cytotoxicity of traditional versus contemporary dental ceramics. J Prosthet Dent. 2003;90(5):452-8.
27. Pandoleon P, Bakopoulou A, Papadopoulou L, Koidis P. Evaluation of the biological behaviour of various dental implant abutment materials on attachment and viability of human gingival fibroblasts. Dental Materials. 2019;35(7):1053-63.
28. Sabaliauskas V, Juciute R, Bukelskiene V, Rutkunas V, Trumpaite-Vanagiene R, Puriene A. In vitro evaluation of cytotoxicity of permanent prosthetic materials. Stomatologija. 2011;13(3):75-80.
29. Cvikl B, Hess SC, Miron RJ, Agis H, Bosshardt D, Attin T, et al. Response of human dental pulp cells to a silver-containing PLGA/TCP-nanofabric as a potential antibacterial regenerative pulp-capping material. BMC Oral Health. 2017;17(1):1-10.
30. Ansteinsson V, Kopperud H, Morisbak E, Samuelsen J. Cell toxicity of methacrylate monomers—The role of glutathione adduct formation. Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials. 2013;101(12):3504-10.
31. Krifka S, Spagnuolo G, Schmalz G, Schweikl H. A review of adaptive mechanisms in cell responses towards oxidative stress caused by dental resin monomers. Biomaterials. 2013;34(19):4555-63.
32. Atalayin C, Armagan G, Konyalioglu S, Kemaloglu H, Tezel H, Ergucu Z, et al. The protective effect of resveratrol against dentin bonding agents-induced cytotoxicity. Dental materials journal. 2015;34(6):766-73.
33. Sjogren G, Sletten G, Dahl JE. Cytotoxicity of dental alloys, metals, and ceramics assessed by millipore filter, agar overlay, and MTT tests. J Prosthet Dent. 2000;84(2):229-36.
34. Shahbazian H, Absalan A, Jalali MT, Mastipour F, Kaydani GA, Zayeri ZD. Comparison of zinc, copper, selenium, magnesium, aluminium and lead blood concentrations in end-stage renal disease patients and healthy volunteers in Ahvaz, southwest of Iran. Russ Open Med J. 2018.
35. Ahmadipour F, Mahjoub S, Pouramir M, Siahposht A, Naderi AA, Absalan A. Determining Serum Zinc and Magnesium Levels in Hemodialysis Patients Could be Helpful for Clinicians. Indian journal of clinical biochemistry : IJCB. 2016:1-4.
36. Abo-Hamar S, Etman W. Effect of repeated bleaching by low hydrogen peroxide regimens–with and without MI Paste Plus–on enamel hardness and composition. Tanta Dental Journal. 2014;11(2):114-21.
37. Hussain B, Thieu MKL, Johnsen GF, Reseland JE, Haugen HJ. Can CAD/CAM resin blocks be considered as substitute for conventional resins? Dent Mater. 2017;33(12):1362-70.
38. Han J, Zhang F, Van Meerbeek B, Vleugels J, Braem A, Castagne S. Laser surface texturing of zirconia-based ceramics for dental applications: A review. Materials Science and Engineering: C. 2021:112034.
39. Porojan L, Vasiliu R-D, Bîrdeanu M-I, Porojan S-D. Surface Characterization and Optical Properties of Reinforced Dental Glass-Ceramics Related to Artificial Aging. Molecules. 2020;25(15):3407.
40. Contreras LPC, Dal Piva AMO, Ribeiro FdC, Anami LC, Camargo SEA, Jorge AOC, et al. Effects of manufacturing and finishing techniques of feldspathic ceramics on surface topography, biofilm formation, and cell viability for human gingival fibroblasts. Operative dentistry. 2018;43(6):593-601.
41. Ramaglia L, Capece G, Di Spigna G, Bruno M, Buonocore N, Postiglione L. Effects of titanium surface topography on morphology and in vitro activity of human gingival fibroblasts. Minerva stomatologica. 2013;62(7-8):267-80.
42. Petrini M, Pierfelice TV, D'Amico E, Di Pietro N, Pandolfi A, D'Arcangelo C, et al. Influence of Nano, Micro, and Macro Topography of Dental Implant Surfaces on Human Gingival Fibroblasts. International Journal of Molecular Sciences. 2021;22(18):9871.