Dental Research Journal

Review Article

Biocompatibility of composite resins

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Received: August 2011
Accepted: September 2011

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ABSTRACT

Dental materials that are used in dentistry should be harmless to oral tissues, so they should not contain any leachable toxic and diffusible substances that can cause some side effects. Reports about probable biologic hazards, in relation to dental resins, have increased interest to this topic in dentists. The present paper reviews the articles published about biocompatibility of resin-restorative materials specially resin composites and monomers which are mainly based on Bis-GMA and concerns about their degradation and substances which may be segregated into oral cavity.

Key Words: Biocompatibility, dental resin composite, fissure sealant

INTRODUCTION

Biocompatibility of dental materials is an important consideration for the patient, clinician, laboratory technician, and manufacturer.

Ideally, a dental material that is to be used in the oral cavity should be harmless to all oral tissues, gingiva, mucosa, pulp, and bone. Furthermore, it should contain no toxic, leachable, or diffusible substances that can be absorbed into the circulatory system, causing systemic responses, including teratogenic or carcinogenic effects. The materials should also be free of agents that could elicit sensitization or an allergic response in a sensitized patient.

RELEASE OF SUBSTANCES

Various components may be released from resin composite restorations into the oral environment.

Therefore the nature and quantity of substances which may be segregated into oral cavity should be known.

There are some reports about leaching substances from dental composite resins and concerns on their biocompatibility which can affect growth and immune responsivity of gingival fibroblasts.[1-4] In permanent teeth, dental resin composites are the most important tooth colored filling materials, in the primary dentition fissure sealants, conventional as well as resin-modified glass ionomer cements, and compomers also play an important role.

There are two main mechanisms which may cause a release of substances from polymeric materials: firstly unbounded monomers and/or additives are eluted by solvents after setting and secondly leachable component are created by degradation or erosion over time. The polymer degradation may be caused by hydrolysis or enzyme catalysis. In general, degradation of a polymer is defined as a chain scission process during which polymer chains are cleaved into oligomers and in special cases finally into monomers, whereas erosion is the loss of materials from the polymer.

The intrusion of water or a solvent following water or other solvent sorption triggers the chemical degradation which results in the formation of oligomers and monomers.[5]

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Different amounts of substances may be eluted from resin composites made by different manufacturers.[6]

There are different methods for quantification of the eluted monomers from resin composites.[7]

Some studies investigated a possible correlation between degree of conversion (DC) and solubility; in contrast to these studies, Ferracane concluded that factors other than DC more significantly influence elution.[8]

Dental composites are complex mixed materials which generally consist of an organic polymerizable matrix, reinforcing fillers, which are mainly inorganic and a silane-coupling agent.[9] The polymerizable matrix contains one or more monomers: e.g., Bis GMA and/or UDMA, co-onomers (EGDMA,DEGDMA,TEG-DMA) and various additives, like an initiator (camphorquinone), coinitiator (e.g., dimethyl–aminobenzoicacidester), an inhibitor of polymerization (e.g., BHT), and a photostabilizer (e.g., benzophenone), various inorganic materials are used as fillers: quartz, borosilicate, lithium aluminum silicate glasses, and amorphous silica. In order to achieve radiopacity, oxide glasses with barium, strontium, zinc or other metals are added to fillers of modern resin composites.[10]

Substances derived from fillers have been determined; correspondingly, all of these studies revealed that mainly barium-containing glasses were susceptible to leaching of this ion from polymerized composite in water, whereas quartz fillers were significantly more stable in an aqueous environment.[11,12] It has been emphasized in a study that the leaching of inorganic ions into water from the fillers varied depending on filler composition and filler treatment.[13]

Biologically active compounds have been identified in the substances, leached from the cured resin matrix. It has been suggested formaldehyde, which is a by-product of polymerization, may be responsible for oral lickenoid reactions.[14,15]

Particular emphasis is placed on the selection of the monomer resins, the filler content, and degree of monomer conversion after the clinical materials are cured.[16]

The effects of matrix selection, filler composition, and filler leachability after storage in distilled water or artificial saliva during a 1- and 3-year periods have been studied; the results revealed that storage solution, filler composition, and total time in the storage solution had strong effects on leachability. The Ba containing filler leached faster in artificial saliva than in distilled water, and roughly twice as much as quartz filler. The tendency of composite to leach filler elements was linear with time and has proposed the incorporation of therapeutic elements such as fluoride in filler particles.[17-20]

Bacterial function is affected by the nature of dental materials as it has been shown in studies that the release of calcium, magnesium, and fluoride from glass ionomers is capable to produce changes in *Streptococcus mutans* metabolism.[21-23]

Effects of copolymer hydrophilicity on water sorption and solubility characteristics of dentin adhesives have been studied to overcome their consequence on durability of resin dentin bonds. The resin coating technique increases durability and bond strength of simplified step adhesives to resin composite.[24]

LOCAL TOXICITY AND TISSUE COMPATIBILITY

Rarely, unintended side effects may be caused by dental restorative materials as a result of toxic, irritative, or allergic reactions that may be local and/or systemic.

Local toxicity is based on the chemical interaction of a toxic substance with biologically relevant molecules while tissue compatibility may also be dependent on causes other than material toxicity.

Local reactions involve the gingival mucosal tissues, pulp, and hard tooth tissue including excessive wear on opposing teeth from restorative materials.

Kanca presents a proposal to alter the current biocompatibility testing methods to methods that can distinguish between the effects of materials and the effects of bacteria on the pulp.[25]

Studies done on hybridization of vital dentin using cohesive bonding systems with definitive restorations and also on healing of exposed pulps in direct contact with various dental materials demonstrated that effectiveness of vital dentin hybridization on postoperative sensitivity control. Exposed dental pulps possess an inherent healing capacity when are adequately sealed with zinc-oxide eugenol cement to prevent bacterial microleakage.[26,27]

Results of a study indicate that the nine tested adhesive systems and resin composites were nontoxic

to either nonexposed or exposed pulps, being biologically compatible to pulp tissues when placed on mechanical pulp exposures following hemorrhage control and placed according to the manufacturer's directions.[28,29]

Fluoride-releasing resin biocompatibility is comparable to that of nonfluoride dental resin. Therefore it can be considered as a biologically safe material as an adhesive or a dental restorative resin.[30] On the contrary another study results revealed that a light-cured, experimental fluoride composite resin with fluoride exhibited maximum relative toxicity compared to FUJI (type II glass ionomer cements) and an experimental fluoride-releasing composite resin while the KETAC-CEM exhibited the least toxicity.[31] Glass ionomer cements, compomers, and giomers are capable to release and re-release after uptake different amounts of fluoride into storage media.[32,33]

Restorative resins are cytotoxic before polymerization and immediately thereafter. Set restorative resins have mild cytotoxicity compared to freshly mix even after three exchanges of the extract.[34] When glass–ionomer cements (GICs) were first introduced, with just one acid (polyacrylic), pulpal responses were classified as bland. With the addition of many more acids to enhance certain characteristics and reduce the setting time, GICs have become more irritating.

A copolymerized new resin composite, in which the filler particle trimethylolpropane-trimethacrylate is chemically bonded to the resin matrix, demonstrated no pulpal irritation or inflammation when was placed on vital dentin of teeth with complete enamel removal.[35]

Unpolymerized resin monomers in resin-modified glass–ionomer cements and Cu^{2+} and Ag+ in metal-reinforced glass ionomer are responsible for cytotoxicity of these materials.[36] The biocompatibility of a fast-setting glass–ionomer cement assessed in a comparative biological study concluded that Ketac-bond is an acceptable restorative material.[37]

A study results indicate that resin-modified glass ionomer and resin composite despite showing some degree of biocompatibility interfered with the development of new bone and the connective tissue attachment process.[38]

Bis–GMA/TEGDMA-based composite resins and 4-META/MMA-based resin cements show better biocompatibility compared to 2-hydroxy-ethyl-methacrylate (HEMA) containing resin modified glass ionomer, suggesting the two former resins to show smaller influence on regeneration of periapical or periodontal tissues.[39] Higher microleakage in experimental adhesives containing Nanoclay fillers is probably related to the high concentration of HEMA in the recipe of the bonding agent.[40]

Determined toxicity of the primers related to two orthodontic adhesives assessed on *in vitro* three-dimensional reconstructed human oral epithelium (RHOE) displayed toxicity for both primers and mild changes after topical application of polymerized adhesives.[41]

Data of a research evaluated immunochemistry, morphologic, and morphometric pulpal alterations of human teeth pulps capped with self-etching or total-etching adhesive systems confirm biocompatibility of self-etching or total-etching adhesive systems when placed directly on dentin.[42]

Production of wear particles following mechanical degradation is important from clinical standpoint. Contemporary dental composites show good resistance to intraoral wear even over long periods of time with a low potential cytotoxicity resulting from the ingestion of wear debris.[43]

BIODEGRADATION OF RESIN MATERIALS

Information about uptake, distribution, metabolism, and excretion of substances released from resin-based composite can help to understand biodegredation of these substances. In some researches the elution of the residual monomers, Triethylene glycol dimethacrylate, and bisphenol-a-glycidyl dimethacrylate from polymerized dental composite was studied. The results revealed that urethane dimetacrylate based composite was less water soluble than Bis GMA materials and some compounds like Bis GMA, UNMA, TEG-DMA, methyl methacrylate monomers especially TEG DMA can be detectable in the water and/or methanol extracts. Most organic substances can be extracted from a set resin by organic solvents; therefore it may be concluded that the extractable quantities of residual monomers and additives should be minimized, either by reducing the mobility within the set restoration by a higher degree of curing or by reducing the release by applying less water soluble monomers and polymerizable or polymer additives.[44-47]

In composite extracts with organic solvents, trace

elements of stabilizer benzophenon as well as fragments of initiator benzoyl peroxide have been determined.[48] In all methanol extracts from various resin composites, the photoinitiator camphorquinone (CQ) was found by some researchers.[6] Extracts from hybrid resin composites contained the photoinitiating substances benzil (BL) and dimethoxbenzoine (DMBZ). Furthermore, these authors reported that all additives could be extracted with methanol, but only very small quantities were detectable in the water extracts, like camphorquinon. Additionally various components arising from polymerization have been found in methanol extract from set resin composites.

Reduction in cytotoxicity of two resin-modified glass–ionomer cements (RM-GICs) after ethanol elution of HEMA and Triethylene glycol dimethacrylate (TEGDMA) from Vitremer and Compoglass suggest that the principal compounds responsible for cytotoxicity are unpolymerized resin monomers in the two RM-GICs and Cu^{2+} and Ag+ in the M-GIC.[36]

Some findings suggested that the higher degree of cure of UEDMA/TEGDMA-based composites would be reflected in a lower monomer leaching value.[49]

During the first 24 hours after polymerization several components especially triethyleneglycol di-methacrylate (TEGDMA), and the "hydrophilic" monomer, 2-hydroxy-ethyl-methacrylate (HEMA), are leached out from various composite resins and "adhesive" materials into the oral environment.

ALLERGIC REACTIONS

Absorption of organic substances from unpolymerized material and also unbound resin components may leach into saliva during the initial phase after polymerization may predispode both patients and dental personnel to allergic reactions.[50] Systemic reactions are expressed generally as allergic skin reactions. Side effects may be classified as acute or chronic.

It is believed that in order to assess the biocompatibility of dental materials, clinical studies, as well as *in vitro* studies, are needed.[51]

Some brands of dental restorative materials possess the ability to release histamine from human blood basophile in sensitive patients.[52]

In recent years, investigators have conducted studies to determine the influence of composite materials and their leachable products on cell growth and function.

Sanerre and colleagues have reported that degradation of dental composites can be regulated by appropriate formulations of the resin chemistry.[53]

Improvement of dental restorative materials is advised because the cytotoxicity of materials undergoing accelerated aging is relevant.[54] Composite restoratives based on ormocers of amine or amide dimethacrylate trialkoxysilane show improved biocompatibility due to lower cytoxicity of ormocers.[55]

Composite –thiolene formulations exhibit improvement in methacrylate conversion and water solubility and are expected to exhibit improved biocompatibility compared to composite dimethacrylate.[56]

Recently silorane-based resin composites have been introduced into the market. Although a study claims that silorane-based and methacrylate-based resins present similar biocompatibility, another study results show less cytotoxicity for silorane-based compared to methacrylate-based resin composites.[57,58]

A low cytotoxicity profile of expanding spiroorthocarbonate monomers suggests their potential for development of biocompatible nonshrinking composites.[59]

An *in vivo* study on the cytotoxic effect of quaternary ammonium polyethylene imine (QA-PEI) nanoparticles revealed no inflammation response 1 week after the implantation of restorative resin composite containing QA-PEI particles.[60]

Calcium hydroxide containing products are the materials of choice to be placed in direct contact with the pulp, prior to placement of restorative resins. The resin-base system incorporating calcium hydroxide represents characteristics of a biocompatible resin in direct contact with vital tissue.[61]

A study tested the outcome of the deposition of particles of dental restorative material in rabbit lungs. The chronic inflammation in the lungs of rabbits indicates a need to test dental restorative material for lung biocompatibility.[62]

In an intraosseous biocompatibility test after 4 weeks vitremer, a new hydrophilic glass–ionomer cement implants showed very slight to slight reactions, and the super ethoxybenzoic acid (EBA) implants showed slight reactions by implantation into the mandible of rabbits.[63]

The cytotoxicity and the fluoride release of two resin-modified glass ionomers, a conventional glass-

ionomer cement, and a resin composite tested by means of 3T3 mouse fibroblasts showed low cytotoxicity for all materials and extraction times indicating minimal cytotoxicity of all materials. Fluoride release and cytotoxicity were correlated, although the fluoride release does not account for the cytotoxicity observed.[64]

ESTROGENICITY

Some polymers used in dental practice contain Bisphenol A, and there are some reports about the estrogenicity of bisphenol A. Estrogen is a natural female hormone that promotes estrus and stimulates the development of secondary female characteristics.[65,66]

From a toxicological standpoint, the migration of oligomers, monomers, and the precursors of synthetic polymers and the other low weight molecules from polymer networks must be carefully controlled, because some of them react with biologically important molecules. This is the case with BPA and bisphenol A diglycidylether (BA BGE) which form adducts on DNA. BPA also binds the estrogen receptors. Bisphenol A was first shown to be estrogenic in 1938, using ovariectomized rats by (Dodds and Lawson, 1938) and then by the other researchers.[67] Bisphenol A was found to be estrogenic in the Mcf-7 human breast cancer cells culture assay. It can also act as an antiandrogen, blocking the action of dihydrotestostrone in a yeast screen containing a human androgen receptor, although some researches indicate that dental resins in general do not represent a significant source of bisphenol A (BPA) or bisphenol A dimethacrylate (BAD) exposure.[68,69]

Lewis propose that a simple *in vitro* method could be used as an alternative or second-line screen for potential xenoestrogens which shows biological estrogens can successfully compete with the antiestrogen in a dose-dependent manner.[70] On the other hand some studies posses the need to use lists of hormonally active chemicals with care.[71]

The sources of human exposure to bisphenol A are cans, can coatings, adhesives, industrial protective coatings, printed circuit boards, industrial floorings, polycarbonate bottles, and dental exposure.[72]

In a study it has been indicated that an increased sensitivity to BPA during the prenatal period suggests the need for careful evaluation of the current levels of exposure to this compound.[73]

Olea *et al*. had found that a sealant based on bisphenol A diglycidyl ether methacrylate (bis GMA) increased cell yields, progesterone receptor expression and PS_2 secretion in human estrogen target, serum sensitive MCF_7 breast cancer cells. They also collected samples of saliva from 18 subjects treated with 50 mg bis GMA-based sealants applied on their molars before and after treatment. They concluded that use of bis GMA-based resins in dentistry and particularly the use of sealants in children appears to contribute to human exposure to xenostrogens.[74] Schafer *et al*. confirmed that BPA and BPA-DM cause cell proliferation at micromolar concentrations that exceed the effective concentrations of estrogen by 1 to 10,000-fold.[66]

Based on a study by Imai bisphenol A contents in the unpolymerized composite resins were 1.5-10.2 µg/g resin.[75]

A study on diphenylalkane derivatives concluded that the hazardous effects of inadvertent exposure to bisphenol A releasing chemicals in professional workers and the general populations deserve investigation.[76] Also the mammalian test system showed root canal sealers containing formaldehyde and bisphenol A diglyether proved to be not only cytotoxic but also genotoxic.[77]

However some researchers have debated these results and have concluded that more comprehensive studies should be undertaken to identify the potential of this hazard.[73,78-81]

It is important that we understand the relative risk at the concentrations experienced clinically. Testing at high dosages may produce responses in test animals that are not representative of human clinical responses.[43]

An article demonstrates that although estrogen-like effects of one fissure sealant have been claimed, no conclusions can be drawn at present for the patient from these *in vitro* data because of the limitation of the test methods and materials used.[82]

The American dental association concern about these research results led to conduct its own evaluations. According to these investigations it revealed that of the 12 brands of dental sealants that carry the ADA seal of acceptance, 11 of the 12 materials leached no detectable Bisphenol A on first analysis. On second analysis, one sealant (BPA) leached a trace amount of BPA within the test sensitivity (five parts per billion). After additional quality control in the manufacturing

processes, none of the dental sealants that carry the ADA acceptance released detectable BPA.

The ADA also tested the blood of dentists who had dental sealants on their teeth and who did not, BPA was not found in any of the blood samples from either group. In addition ADA worked with researchers at university of Nebraska. Dental sealants were applied to test subjects, and then saliva and blood samples were collected at various time intervals after sealant application.

The results showed that BPA released orally is not detectable at or above 5 ppb when measured in systemic circulation, so that another research corroborates ADA findings.[83]

Finally in a statement ADA council on scientific affairs concluded about the study of march 3, 1996, issue of environmental health perspective, entitled "Estrogeniciy of resin based composite and sealants used in dentistry" that the effect of BA dimethacrylate which is widely used in resin-based composites and sealants appears to be from uncured sealants materials in that study.

In contrast to sealants, that study showed that monomers from uncured composites were not particularly estrogenic when evaluated by the same tests. This finding is probably due to the higher proportion of inorganic filler in composites resulting in lower amounts of monomers in the paste; furthermore these monomers were detected in the saliva of the patient in whom sealants had been applied 1 hour earlier. Monomers were not detected in saliva before sealant placement, so further tests and more clinically relevant experiments would need to be formed before any definitive conclusion can be drawn for these results, because these researchers did not attempt to measure if any released monomers detected in saliva actually enter the bloodstream and or if metabolic degradation of these monomers occurs.

ADA believed that other research reports that 50% of leachable species from a cured composite eluted within the first 3 hours in water would tend to indicate that *in situ* most leachable monomers would be eluted within a short period of time following placement, thus limiting time of exposure to any estrogen-like monomers.[84]

ADA also recommended additional experiments should be encouraged to determine the extent, if any, and duration of leachable monomers in the blood following sealants or composite placement; and to determine the long-term leachability of sealant/composite monomers in the aqueous media, also attempt to duplicate the estrogenic effects of BA and BA- dimethacrylate in normal human cell culture rather than in cancerous cells, and compare the rates of metabolic degradation of BA and BA – dimethacrylate with estradiol.

Dental composite is now used in over 95% of all anterior teeth direct restorations and in 50% of all posterior teeth direct restorations.

Improvement of dental-restorative materials is required to limit the long-term biological damage.[54]

Recently, quaternary ammonium poly (ethylene imine) (QA-PEI) nanoparticles that were embedded in restorative composite resin at 1% w/w resulted in the complete growth inhibition of *streptococcus mutans*.[60]

Different methods have been proposed to evaluate biocompatibility of resin-based dental restorative materials. The quantification method in which combineed gas chromatography-mass spectrometry (GC/MS) with tailor-made internal standards seems well suited for *in vivo* analysis eluted compounds from dental materials into saliva.[7]

The study on degradation of model overlayer-containing Bis-GMA, after being aged in water, by liquid chromatography mass spectrometry demonstrated the absence of bisphenol A release from the overlayer reduces concerns regarding its potential health risk in dental composites.[85]

Milhem *et al*. in an investigation of the effect of extracts of different composites, glass ionomer cement (GIC)s, and compomers on the viability of brine shrimp larvae concluded that the toxicity of composite materials varied according to their chemical composition. Compomers were the most lethal materials to brine shrimp larvae followed by GICs and then composites.[86]

Both the *in vitro* pulp chamber and the mucosal barrier test have distinct limitations. However, biocompatibility is not limited pulp damage or mucosal damage caused by a dental restorative material or to the mutagenic properties.[87]

In order to assess the biocompatibility of dental materials, clinical studies, as well as *in vitro* studies, are needed.[51] Goldberg states that there is a large gap between the results published by research laboratories and clinical reports, because mechanisms of cytotoxicity are related firstly to the short-term release of free monomers occurring during the

monomer–polymer conversion, but long-term release of leachable substances is generated by erosion and degradation over time.[88]

Recent data approve that Bis-GMA/TEGDMA-based composite resin and 4-META/MMA-based resin exhibits better biocompatibility than HEMA-containing resin-modified glass-ionomer.[39]

The findings of the past decade clearly indicate that there are many reasons to probe the issue of biochemical stability of resin composites in the oral cavity. Further researches are needed to fulfill previous findings about biochemical stability of composite resins. The acquired information from such studies will generate the development of alternate polymeric chemistries and composite formulations that will require further investigation for use as the next generation of restorative materials with enhanced biostability.[16]

CONCLUSION

Reviewing data from these studies will help determine if the risk of damage and estrogenic effects of composite monomers and dental sealants have any real clinical consequence. Further researches are needed to investigate biochemical stability of composite resins in the oral cavity which will lead to a more concise definition of biocompatibility related to dental resin composites.

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How to cite this article: Mousavinasab SM. Biocompatibility of composite resins. Dent Res J 2011;8:S21-9.

Source of Support: Nil. **Conflict of Interest:** None declared.