

BIOACTIVE DENTAL COMPOSITE MATERIALS

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Summary

Bioactive dental composite materials offer the potential to prevent secondary caries, which is one of the major causes of failure of contemporary composite restorations. Various experimental formulations of bioactive composite materials are currently being investigated worldwide, although very few commercial products are available for clinical practice. The caries-preventive effect of bioactive composites is attained by two main approaches: antimicrobial activity and remineralization of dental hard tissues. This article provides a brief overview of experimental bioactive composite materials based on amorphous calcium phosphate and bioactive glasses. Their advantages, drawbacks and the most important properties are discussed. Generally, some compromise is always required in balancing the bioactivity and mechanical properties of composite materials. The characteristics of bioactive fillers (composition, particle size, filler loading, surface treatment) need to enable sufficient ion release in an aqueous environment, while not negatively affecting basic properties of composite materials, such as: the degree of conversion, polymerization shrinkage and related shrinkage stress, strength, hardness, elastic modulus, degradation in water and biocompatibility. The major benefits of bioactive composite materials include: the capability to regenerate dental hard tissues after an acid attack by supplying calcium, phosphate and other ions, reduction of dentin hypersensitivity and postoperative sensitivity, precipitation of hydroxyapatite in the marginal gap, inhibition of bacterial growth and improvement in the durability of the bonding between the composite material and dentin.

Keywords: bioactive dental resin composites; remineralizing composites; bioactive glass; amorphous calcium phosphate; remineralization.

DENTAL COMPOSITES

In their inception, dental composites were developed as an aesthetic alternative to dental amalgam and were intended for restorations of anterior teeth, as they were unable to withstand masticatory loads on posterior teeth. These early

composites suffered from various issues such as low abrasion resistance, poor mechanical strength and color instability (1, 2). Intensive research that followed in the field of dental composites has led to highly improved material properties (3). Mechanical properties of contemporary composites are comparable to those of dental amalgams (4), while their exceptional aesthetic properties cannot be matched by any other material for direct restoration (3). Nowadays, composite materials have become a versatile material class suitable for filling of all restoration classes, as well as the material of choice for direct restorative treatment (5).

Despite significant improvements in the technology of dental composites, their basic composition has not changed significantly since they were first formulated in the 1950's (6). Most of the contemporary composites are basically a mixture of glass and ceramic particles dispersed in a methacrylate resin comprised of bifunctional monomers (7). The glass/ceramic particles are coated with a coupling agent, usually silane, which allows them to chemically bond with the methacrylate network during the hardening process of the composite (8). The setting reaction of dental composites occurs via free radical polymerization, which was in early composite formulations initiated chemically but was soon replaced by a more convenient activation by visible light, which represents the predominant activation technique in contemporary composites (9). The visible light activation is highly beneficial since it gives the clinician enough time to manipulate the material and sculpt the restoration to the appropriate form before initiating the setting reaction.

An inherent drawback of all dental composites is their volumetric shrinkage which takes place when the material polymerizes and the intermolecular distances between monomer molecules convert into shorter covalent bonds (10). This process causes the formation of microgap between the composite restoration and cavity walls, which can be infiltrated by oral bacteria (11). As some of these bacteria produce acids, the demineralization occurs at the interface between the cavity and composite restoration, leading to the occurrence of secondary caries (12). Despite all of the major improvements in the development of dental composites, the issue of secondary caries remains unresolved and it is often regarded as one of the major causes for failure of composite restorations (13).

SECONDARY CARIES AND BIOACTIVE MATERIALS

The pathophysiology of secondary caries is similar to that of primary caries: the biofilm consisting of multiple bacterial species and their organic products

adheres to the tooth and produces acids that could not be sufficiently buffered by saliva. As the pH value decreases, the equilibrium between demineralization and remineralization of the tooth structure is violated and a net loss of calcium and phosphate ions occurs. In contrast to outer tooth surfaces from which the biofilm can be removed by means of daily oral hygiene, the micrometer-sized gap between the tooth and the restoration is unreachable to mechanical cleansing. This allows the unperturbed development of bacteria within the interfacial gap, leading eventually to secondary caries (14).

The issue of secondary caries is as old as composite restorations and is the primary motivation behind the studies of bioactive composites. This heterogeneous group of materials employs different strategies with the common aim of preventing secondary caries. Their bioactive effects can be divided into two main groups: antimicrobial activity and remineralization (15,16). The former is attained by the addition of various antibacterial components (chlorhexidine, tertiary ammonium compounds, silver ions and antibacterial monomers) to the composite, while the latter is based on soluble fillers which release calcium, phosphate, fluoride and other ions (17). These ions can be incorporated into demineralized dental hard tissues (18,19) or precipitated within the defects at the interface between the tooth and the restoration, thereby contributing to its sealing (20). Different combinations of antibacterial and remineralizing effects are also being investigated (21).

BIOACTIVE COMPOSITES BASED ON AMORPHOUS CALCIUM PHOSPHATE

Various calcium phosphates [monocalcium phosphate, dicalcium phosphate, tricalcium phosphate, hydroxyapatite (HA) and amorphous calcium phosphate (ACP)] can be used as ion-releasing fillers in experimental composites (16,22-25). Among these compounds, amorphous calcium phosphate (ACP) is interesting because it is a direct precursor of hydroxyapatite (HA), which naturally participates in the developmental mineralization of teeth and bones (26). ACP is thermodynamically unstable due to its unordered structure and upon water exposure transforms into HA, concomitantly releasing calcium and phosphate ions (27). This process is the basis of the ACP bioactivity and can be exploited to produce remineralizing composite materials (28).

ACP conversion and ion release

The conversion of ACP into HA is essentially a dissolution/reprecipitation process. As the initial ACP particles are gradually dissolved, calcium and phosphate ions are solubilized and subsequently precipitated in the form of HA (29). As the conversion advances, the HA precipitate forms an envelope-like layer around the original ACP particles (30). The ACP/HA conversion proceeds autocatalytically because the already formed HA acts as nuclei for further crystallization (31). This is the reason for the high instability of pure ACP in aqueous media and its tendency to readily convert into HA within several hours (32). In order to retard the conversion and attain a longer-lasting bioactive effect, ACP particles can be hybridized with zirconia. Zirconia interferes with ACP crystallization by blocking potential sites for HA nucleation and growth (33). An additional benefit of modifying ACP with zirconia was an improvement in mechanical properties (34). Embedding ACP particles into a methacrylate resin additionally slows down the conversion and allows their use as bioactive fillers in dental composite (27).

The ion release from ACP fillers is a function of multiple factors, some of which are: environmental pH, temperature, ACP hybridization and resin matrix hydrophilicity (29,31,35,36). The ion release of experimental ACP-based composites is traditionally judged by the concentration of calcium and phosphate ions released in an aqueous medium. Thus ACP-containing composites which can produce calcium/phosphate solutions supersaturated with respect to HA are considered to be able to remineralize dental hard tissues (37).

Mechanical properties

Experimental composites filled with micrometer-sized ACP particles commonly show inferior mechanical properties in comparison to contemporary commercial composites (38). This is primarily caused by a high loading of ACP particles which is required to attain the bioactive effect – approximately 40 wt% of ACP fillers is required for an ion release sufficient for remineralization (37). The initially low cohesive strength of ACP fillers is further diminished with aging in water, as the filler particles gradually dissolve within the composite structure and their constituents re-precipitate in the form of HA. Uncontrolled agglomeration of ACP particles is another factor contributing to their poor mechanical properties (28). Moreover, ACP particles must not be silanized as the

silane layer would interfere with their ability to release ions (39). The unsilanized surface renders the ACP fillers unable to bond to methacrylate network. As such, ACP particles cannot act as reinforcing fillers and instead weaken the composite structure. This is illustrated by the fact that the ACP-filled composite presented half the strength of the neat copolymer with which it was formulated (40).

Mechanical properties of ACP-composites can be improved by the admixture of inert glass fillers, which are similar in composition and properties to those used in commercial composites (41). These fillers are silanized and stable in aqueous medium, providing mechanical reinforcement while the weaker ACP fillers are being gradually dissolved and converted into HA (23). The addition of 10 wt% of reinforcing fillers was demonstrated to increase mechanical properties without adversely affecting the ion release of experimental composites containing 40 wt% of ACP (23,41,42). The degree of conversion and light transmittance were also unimpaired by the addition of reinforcing fillers, while the polymerization shrinkage was reduced (23,43).

An alternative and very successful approach to improving mechanical properties of ACP-composites is by reducing the particle size of bioactive fillers (15). This is made possible by preparing nano-sized ACP fillers via spray-drying technique, instead of the traditional preparation in which ACP was precipitated upon mixing of saturated calcium and phosphate solutions (44). The benefits of using nano-sized ACP are twofold: first, small particles have less impact on the mechanical properties as they produce smaller defects of low cohesive strength within the material structure; and second, the high specific surface area of small particles enables sufficient ion release with lower loading of ACP fillers (45). This means that higher amounts of reinforcing fillers can be included in the composite, resulting in exceptional improvements of mechanical properties. The experimental composites based on nano-sized ACP fillers demonstrated mechanical properties comparable to those of conventional composites (15,45).

Degree of conversion

As the fundamental property which affects practically all other properties of a composite material, the degree of conversion should generally be kept as high as attainable (9). The main limiting factor for reaching high degrees of conversion is an immense increase in viscosity in the composite during polymerization. High viscosity impairs mobility of free radicals and monomers, causing the polymerization reaction to stop well before all available reactants are consumed

(46). The conversion of conventional composites usually reaches 50-75% (47), while ACP-composites were repeatedly shown to attain high conversions, reaching up to 87% (48-50). High conversion observed in experimental ACP-composites can be attributed to the high mobility of their resin systems, as well as the presence of high filler load of unsilanized particles which apparently act to improve the mobility of monomers and free radicals (43,50). Another important feature of polymerization in ACP-composites is a very high degree of conversion attained immediately after light irradiation, with very low extent of the post-cure conversion increase (50). This suggests that the ACP-composites attain very high biocompatibility immediately after light curing, unlike commercial composites with post-cure conversion increase reaching up to 40% (51).

Despite the whitish, opaque appearance of ACP-composites, their ability to transmit curing light is comparable or even better than that of commercial composites (43). Using the standard curing protocol (20 s with an irradiance of 1000 mW/cm²), ACP-composites can be adequately cured in a layer of 2 mm, which is the standard thickness for conventional composites. By prolonging the curing time to 40 s, the allowed layer thickness increases to 3 mm (50). An important finding is that the addition of inert fillers does not considerably affect the degree of conversion, meaning that ACP-composites may be reinforced with additional amounts of silanized glass fillers, probably for as much as rheological properties would allow (43,50).

A distinct kinetic behavior during the polymerization of ACP-composites was suggested by the real-time light transmittance measurements (43). Although the appropriateness of the light transmittance monitoring for gaining a detailed and accurate insight into polymerization kinetics is questionable (52), the obtained data suggest that ACP-composites polymerize with significantly different rates than commercial composites. Briefly, ACP-composites appear to have a slower and more gradual polymerization, with lower and sustained polymerization rate, while commercial composites exhibit a sharp peak in polymerization rate caused by a pronounced autoacceleration. This kinetic behavior could be attributed to the better mobility of the reactive medium due to the resin composition and the presence of unsilanized fillers (50). It could be hypothesized that the observed kinetic pattern causes the high final conversion values which are commonly observed in ACP-composites (48,49). The topic of distinct polymerization kinetics in ACP-composites is currently being investigated further by means of direct methods (real-time infrared spectroscopy) and preliminary results have confirmed the aforementioned hypotheses.

Polymerization shrinkage

As the polymerization shrinkage is a function of the amount of converted double methacrylate bonds, the high conversions of ACP composites are inevitably accompanied with high shrinkage (23,28). This is especially pronounced in ACP-composites with high resin to filler ratio (23) as they contain more methacrylate double bonds per a unit of volume. Reducing the resin/filler ratio by incorporating as much reinforcing filler as possible (45) would help to lower the polymerization shrinkage while at the same time benefiting mechanical properties.

Electrical properties

Our studies were the first to investigate electrical properties of ACP-composites by means of impedance spectroscopy (53). Electrical properties are not routinely studied in dental composites, as they lack clinical relevance due to composite's insulating characteristics. However, electrical measurements can be used to probe material microstructure and to gain indirect information about other properties. For example, the decrease of electrical conductivity during curing can be used to assess the polymerization kinetics, the correlation of electrical conductivity with water amount in a composite can be used to quantify the water introduced into the material by the hydrophilic ACP particles and electrical properties can be used to differentiate various particle sizes (53). Additionally, real-time conductivity measurements can be useful for assessing the integrity of material structure during the setting reaction (54).

Evidence of bioactive behavior

In addition to the purely chemical proof of the remineralizing capability, the bioactive potential of ACP-composites was demonstrated *in vitro*, *in situ* and *in vivo* (55-57). Under *in vitro* conditions, artificially prepared caries-like subsurface enamel lesions restored with ACP-composite were subjected to a cyclic remineralization/demineralization procedure. The remineralizing effect of the ACP-composite was four-fold higher than that of the fluoride-releasing commercial composite (55). *In situ* experiment used cavities prepared in bovine enamel, restored with an ACP-based composite and exposed to cariogenic conditions. The restored enamel slabs were mounted in palatal devices worn by volunteers and the study concluded that caries formation was substantially reduced in ACP-composites

compared to the commercial control composite (56). The *in vivo* study used a rat cavity model and demonstrated a milder pulpal inflammatory response as well as the greater formation of tertiary dentin compared to the control composite (57). All of these studies used nano-sized ACP fillers which appear as a good alternative to the traditional micro-sized fillers.

Commercial products

Up to now, only one ACP-containing composite material intended for the bonding of orthodontic brackets has been commercialized. However, its production was discontinued due to poor mechanical properties and low bond strength (58). Thus there are currently no commercial ACP-based composite materials available, but casein phosphopeptide-stabilized ACP is being extensively used as a topical remineralizing agent in tooth mousse preparations (59), post-bleaching remineralizing gels (60) and even chewing gums (61).

BIOACTIVE COMPOSITES BASED ON BIOACTIVE GLASS (BG)

BG as filler in dental composites

BGs pertain to the group of soluble glasses mainly composed of SiO_2 , CaO , Na_2O and P_2O_5 in variable ratios (62). The solubility and thus bioactivity of BGs are determined by their composition and small compositional adjustments can be made to tailor materials suitable for specific applications (63). The BGs have a long-standing history of use in orthopedics, as coatings for bone implants due to their ability to spontaneously precipitate HA and facilitate osseointegration (64). The potential to release remineralizing ions and precipitate HA makes BG a potential source of remineralizing ions in experimental dental composites.

When exposed to water, BG undergoes a series of reactions which lead to the formation of HA. Initially, the BG surface exchanges sodium and calcium ions with hydrogen ions from the solution, creating Si-OH groups and forming a silica-rich (sodium/calcium-depleted) layer. As the local pH increases, the Si-O-Si bonds are attacked by the hydroxyl ions and silica is dissolved in the form of $\text{Si}(\text{OH})_4$. As the Si-OH groups condense, the silica-rich layer is repolymerized, attracting calcium and phosphate ions to precipitate in the form of ACP, which subsequently crystallizes into HA (62). The described processes have several effects which could be exploited in dental composites: (I) release of reminerali-

zing ions, (II) decrease of the local pH, and (III) HA precipitation (20,65,66). For this to happen, the composite structure must allow water to reach BG particles and the ions must be able to leach out of the composite structure. Thus resin hydrophilicity needs to be adjusted appropriately and BG particles must not be coated with a silane layer (67).

Remineralizing effect

Composite materials based on BG can release calcium and phosphate ions to remineralize dental hard tissues in a similar manner to the ACP-based composites. The BG particles exhibited the remineralizing ability whether they were applied directly to the artificially demineralized dentin (68) or incorporated into a methacrylate resin resembling the composition of adhesive systems (69). The remineralizing effect on the enamel was demonstrated in a study in which artificial white spot lesions were successfully remineralized with a direct application of either unmodified or polyacrylic acid-modified BG (19). However, a concern has been raised regarding the clinically relevant benefit of dentin remineralization in terms of improvement in mechanical properties, as the higher amount of HA in dentin does not necessarily strengthen its structure (66). In order to improve dentin strength, the HA deposition has to occur in the collagen matrix intrafibrillary, because the extrafibrillar mineralization does not contribute to mechanical properties. This issue should be clarified in further studies.

Antibacterial effect

The antibacterial effect of BG originates from the pH raise during their dissolution. The reduction of bacterial viability was observed by pure BG and by eluates obtained from BG, confirming that the antibacterial effect is not necessarily related to the contact toxicity but rather to the pH change in the solution (65). As neutralization of the eluates negated the antibacterial effect, it could be ascribed solely to the pH increase (65,70). The possibility of modifying the BG composition by the addition of various trace components allows formulating of various BGs with improved antibacterial properties. For example, silver-containing BG exerts a direct toxic effect on bacteria in addition to the aforementioned pH changes (71). This silver-modified BG also showed an antibacterial effect when incorporated in a methacrylate matrix of a commercial resin composite (72).

Marginal gap sealing

Sealing of the marginal gap is made possible by the distinct feature of BG to form HA layers at their surfaces (63). Although the experimental composites based on ACP and other calcium phosphates are also capable of precipitating HA (42), in these materials the ion release dominates over reprecipitation and most of the remineralizing ions are lost in the solution. In contrast, the hydrated silica on the BG surface provides nucleation sites for HA, favoring its precipitation almost immediately after the start of dissolution. This feature can be used to form an HA layer on the restoration surface which is thick enough to hinder bacterial penetration into the marginal gap (20). This very promising effect should be further investigated regarding the stability of the HA layer created within the gap and its resistance to the cariogenic environment.

Treatment of dentin hypersensitivity and postoperative sensitivity

The precipitation of HA can occlude dentin tubules and reduce the dentinal fluid flow, thus diminishing painful symptoms of hypersensitive dentin (73). Toothpaste was shown as an effective medium for the delivery of BG particles (74) and a brand of toothpaste containing patented BG particles is commercially available (75). It is expected that a similar effect of obliteration of dentinal tubules could be attained by BG-containing restorative materials or adhesives, which could help in reducing the postoperative sensitivity after placing composite fillings.

Improving the longevity of the hybrid layer

The durability of the interface between the composite restoration and dentin is currently the weakest point of otherwise very successful composite materials (76). Despite extensive research efforts to improve the strength of bonding to dentin and reduce its degradation over time, this goal is far from being accomplished (77). The bioactive effect of BG-containing composites could increase the longevity and stability of the hybrid layer by at least two effects: by inhibiting the matrix metalloproteinase activity via the increase in the local pH and by depositing the HA precipitate within the demineralized collagen network (78,79), thus decreasing the nanoleakage and protecting the hybrid layer from hydrolytic degradation (80).

Biomimetic remineralization

An interesting approach of biomimetic remineralization attempts to improve the durability of the hybrid layer by mimicking the naturally-occurring mineral deposition within the collagen scaffold. Polyanionic molecules are used which function similarly to the non-collagenous dentin proteins and provide a template for HA deposition within the collagenous network (81). In the process of biomimetic remineralization, the water surrounding collagen fibrils is progressively being replaced by both intrafibrillar and extrafibrillar HA precipitation which provides unmatched stability of collagen, comparable to that of the dentine mineralized naturally during its development (82). Among different potential sources of calcium and phosphate ions for biomimetic remineralization, neat BG and BG-filled resin composites or adhesives have been proposed (83). The biomimetic remineralization strategy may be advantageous over other approaches to improve dentin bond durability (e.g. modifications of monomers, usage of collagen crosslinkers and matrix-metalloproteinase inhibitors), as it addresses the issue at its very origin by removing the water from the hybrid layer and rendering all the degradation mechanisms ineffective (83).

Commercial products

Besides its successful application in orthopedics, BG is also used as a remineralizing agent in dentistry: toothpaste for treating dentin hypersensitivity (75) and air abrasion powder (68) are available commercially. However, no dental composites or adhesives containing BG have been commercialized yet.

CONCLUSION

In the current phase of development, dental composites have reached a stage at which further improvements of mechanical properties would probably not contribute much to the clinical success and longevity of composite restorations. In contrast, the lingering issue of interfacial microleakage and secondary caries leaves much space for improvements and it could be expected that research efforts would focus towards developing bioactive materials which have been showing promising results in overcoming this problem. The composites based on various calcium phosphates and BG certainly have an important place among bioactive materials and combined with other active compounds (e.g. antimicrobial agents) could significantly contribute to the improvements in the clinical performance of future restorative materials.

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Sažetak

Bioaktivni dentalni kompozitni materijali

Bioaktivni dentalni kompozitni materijali posjeduju potencijal za prevenciju sekundarnog karijesa, koji je jedan od glavnih uzroka neuspjeha suvremenih kompozitnih restauracija. Različite eksperimentalne formulacije bioaktivnih kompozitnih materijala se istražuju diljem svijeta, ali komercijalni proizvodi dostupni za kliničku uporabu su malobrojni. Učinak sprečavanja karijesa kod bioaktivnih se kompozita postiže putem dvaju glavnih pristupa: antimikrobnom aktivnošću i remineralizacijom tvrdih zubnih tkiva. U ovom članku je izložen kratki pregled eksperimentalnih bioaktivnih kompozitnih materijala temeljenih na amorfnom kalcijevom fosfatu i bioaktivnim staklima. Opisane su njihove prednosti, nedostaci i najvažnija svojstva. Općenito, uravnoteživanje bioaktivnosti i mehaničkih svojstava kompozitnih materijala uvijek zahtjeva određeni kompromis. Svojstva bioaktivnih punila (sastav, veličina čestica, udio punila, površinski tretman) trebaju omogućiti dostatno otpuštanje iona u vodenom okolišu, a pri tome ne smiju negativno utjecati na temeljna svojstva kompozitnih materijala, poput: stupnja konverzije, polimerizacijskog skupljanja i s njim povezanog stresa, čvrstoću, tvrdoću, modulus elastičnosti, degradaciju u vodi i biokompatibilnost. Glavne prednosti bioaktivnih kompozitnih materijala uključuju: mogućnost regeneracije tvrdih zubnih tkiva nakon izloženosti kiselini pomoću kalcijevih, fosfatnih i drugih iona, smanjenje dentinske preosjetljivosti i postoperativne osjetljivosti, precipitaciju hidroksiapatita u marginalnoj pukotini, inhibiciju bakterijskog rasta i poboljšanje trajnosti sveze između kompozitnog materijala i dentina.

Ključne riječi: bioaktivni dentalni kompoziti; remineralizirajući kompoziti; bioaktivno staklo; amorfni kalcijev fosfat; remineralizacija.

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