New Advanced Materials for High Performance at the Resin-Dentine Interface

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Abstract

This chapter provides a tool for the integration of new concepts and biomaterials related with the resin-dentine interface. The principles of dentine demineralisation and remineralisation that shape modern restorative dentistry practices, as well as considerations for the selection of new materials for different restorative approaches, are emphasised. Re-incorporation of mineral into the demineralised dentine matrix is important since the mineral precipitated may work as a constant site for further nucleation, and the remineralised subsurface of the tissue may be more resistant to subsequent acid attack. This deposition of minerals may be due to both spontaneous precipitation induced by local supersaturation of Ca and P in the presence of non-specific tissue alkaline phosphatase or through heterogeneous nucleation sites provided by phosphoproteins within the dentine collagen matrix. Nucleation is a multistep process involving both protein and mineral transition and suggests a temporally synchronised process. Dentine provides both structural and chemical frameworks, acting as a scaffold for mineral deposition at specific sites. The ultimate goal in the design and improvement of new materials for high performance at the resin-dentine interface is to render a stronger and durable adhesion to dental tissues despite the severe conditions in the oral environment. In the present chapter, glass ionomers, calcium-phosphate cements and doped dental adhesives have been selected to represent the cutting edge biomaterials at the interface.

Dentine Demineralisation Procedures

Demineralisation of dentine is the process of removing mineral ions from the apatite latticework leaving the collagen fibres without support, except for the water contained within the dentine. Demineralisation of dentine, or dentine conditioning, is used as a first surface preparation step to improve adhesion for a variety of procedures involved in resin-dentine bonding for restorative dentistry; the aim is to improve monomer spreading onto the substrate, and to increase the diffusivity into the dental tissue, in order to get the subsequent entanglement of the adhesive resin into the dentinal components and to achieve the so-called hybrid layer. The hybrid layer is a structure made up of type I collagen fibrils and proteoglycans enveloped by polymer chains. Acidic agents remove the smear layer and the superficial part of the dentine, opening dentine tubules,

demineralising the dentine surface and increasing the microporosity of the intertubular dentine. They also promote wettability by producing increased surface contact area and capillary action due to the erosion of intertubular dentine and enlargement of dentinal tubules through peritubular dentine dissolution. Following acid etching, in addition, some non-collagenous proteins are solubilised and some of the proteins are extracted.

After dentine conditioning with phosphoric acid, the surface energy of dentine decreases due to the exposure of collagen fibres and loss of the mineral component. There is a correlation between the ability to spread on a dentine surface and the concentration of calcium on that same surface. Three important shortcomings are produced: (1) the dentine surface becomes hydrophobic as a result of calcium depletion and collagen fibres become prone to collapse (0.3–0.5 µm of the matrix) impairing resin infiltration; if water or primers are applied on dentine, it becomes more hydrophilic, but resin monomer infiltration is difficult, and inadequate polymerisation of these monomers will occur; (2) dentine demineralisation highly decreases its mechanical properties, and (3) opening of dentinal tubules facilitates upward flow of the fluid. The presence of the aqueous fluid leads to phase separation of resin monomer blends and makes polymerisation difficult, facilitating the hydrolytic degradation of the bonded interface.

Self-etching adhesives were incorporated into clinical procedures to compensate these drawbacks, but they still resulted in a non-infiltrated demineralisation front. Milder conditioners (i.e. ethylenediamine tetra-acetic acid, EDTA) eliminate the smear layer and plugs, causing dentinal erosion, but remove less amount of calcium from the dentine surface, promoting shallow demineralisation and induce favourable chemical modifications that improve dentine wettability and penetration of hydrophilic monomers. The milder demineralisation effect is supposed to leave more residual apatite crystallites within the collagen
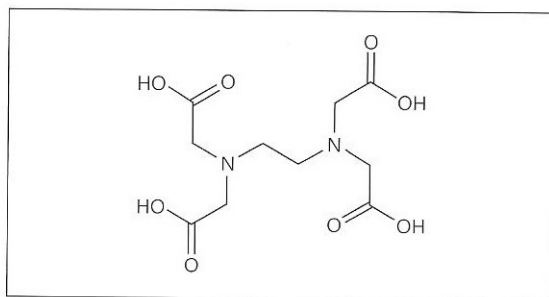

Fig. 1. Ethylenediamine tetra-acetic acid.

matrix [1]. Interestingly, after EDTA conditioning of dentine, roughness does not increase and tubule entrances are not enlarged, but contact angle equally decreases (i.e. wettability increases) compared with phosphoric acid use; thereby, minor changes are expected to occur in the mineral content of dentine surfaces after EDTA conditioning [2]. EDTA is a molecule that contains 4 carboxylic acid groups (fig. 1), and it has the ability to chelate to calcium. It has been widely used to dissolve the mineral phase of dentine without altering dentine proteins, avoiding major alterations in the native fibrillar structure of dentine collagen and facilitating resin infiltration.

As stated before, collagen fibrils contain intra- and extrafibrillar minerals, which completely cover their structure. During demineralisation, the mineral is removed much more slowly from within the collagen fibrils than from the extrafibrillar compartment [3, 4]. Intrafibrillar mineral is rather resistant to demineralisation and thus influences remineralisation, as partially demineralised dentine may contain intact collagen fibrils with remnant mineral plus insoluble non-collagenous proteins in association with the remaining crystallites that could perform as sites for recrystallisation. When EDTA is applied on dentine, the collagen fibrils are thought to retain most of their intrafibrillar mineral; therefore, their structural support is not missed, explaining that intertubular dentine appearance and nanohardness are similar to that of intact (polished) dentine [1].

The maintenance of the intrafibrillar mineral after EDTA treatment of dentine may also explain the improved resistance to degradation of EDTA-demineralised dentine and resin bonds to EDTA-treated dentine. Acidic conditioning may damage, but not denature, the structural integrity of collagen. To improve collagen original integrity, cross-linking and re-inforcement techniques are being introduced [5].

Remineralisation of Dentine

The term remineralisation of dentine refers to the process of restoring the inorganic matrix, which is clinically applicable to prevention strategies, therapy of dentine caries, hypersensitivity, erosion of the cervical area, affected dentine and exposed collagen incompletely infiltrated. This progress physiologically occurs onto demineralised dental surfaces, where the mineral is reabsorbed and damaged crystals are rebuilt. Remineralisation of dentine substrate may depend upon the quality and quantity of the mineral and/or organic component remaining in the structure. Dentine, even in the absence of cells, is able to actively participate in tissue-reparative processes. It contains matrix-bonded bioactive molecules, enzymes and growth factors that may be liberated and activated through different mechanisms in order to complete reparative processes [6, 7].

Biomimetic mineralisation imitates the natural process of mineralisation simulating the original formation process of mineral crystals on the surface of organic and inorganic matrix without using harsh conditions. Pre-nucleation clusters are stabilised first, forming loosely packed negatively charged highly mobile and diffuse structures of apatite nanocrystals that slowly aggregate and densify.

This approach of the remineralisation theory corresponds with the classical (top down) philosophy of mineral growth. Partial demineralisation of a mineralised collagen matrix by acids from bacteria poses an example of a top-down approach in generating seed crystallites as nidi of heterogeneous nucleation. In summary, it is based on the epitaxial growth of residual crystallites, which act as nucleation sites for the calcium phosphate minerals to precipitate when dentine is stored in a solution rich with calcium and phosphate ions. In this case, the precipitation of minerals is extrafibrillar (net remineralisation), without an optimal interaction with the organic component of the dentine matrix, i.e. without the mineralisation of the intrafibrillar compartment of collagen, resulting in an incomplete and non-functional remineralisation of dentine. The net effect may be one of relatively high mineral content, but low mechanical properties, misleading information of the real effectiveness of the remineralisation therapy. On the contrary, the non-classical (bottom-up) approach pursues the hierarchical functionalised biomineralisation of the matrix, involving the use of synthetic substitutes for certain dentine matrix proteins essential for dentine remineralisation. Two analogues may be used for this purpose: the first one requires polyanionic molecules (e.g. polyacrylic acid) to form nano-aggregates of amorphous calcium phosphate $[Ca_x(PO_4)_y]$, and then nanoprecursors with the capacity of infiltrating the water-filled gap zones in dentinal collagen fibrils, precipitating as polyelectrolyte-stabilised apatite nanocrystals Other precursors, such as octacalcium phosphate $[Ca_8H_2(PO_4)_6 \, 5H_2O]$ and tricalcium phosphate $[Ca_3(PO_4)_2]$ phases, have also been identified. The second analogue, a polyphosphate molecule (dentine matrix phosphoprotein substitute), such as sodium metaphosphate, performs as an apatite template, promoting crystalline alignment in the gap zone. Collagen can direct the crystallisation process once it is infiltrated with the amorphous precursor.

To promote a growth centre, the collagen structure should be sound in addition to the presence of residual mineral crystals, which have been identified not only in the demineralised

layer, but also in the region across the demineralised/mineralised dentine. The mineral-inductive capacity of partially demineralised dentine may be explained, complementarily, by the small but definitive fraction of remaining polyanionic proteins (phosphoproteins) strongly attached to the collagenous matrix. The peptides responsible for mineral induction are located between the two collagen binding sites. Removal of the soluble portion of the organic matrix, which contains phosphoproteins, by different decalcifying agents is essential for remineralisation of demineralised dentine. EDTA does not completely remove non-collagenous proteins from dentine, so phosphoproteins are present. Phosphoproteins provide heterogeneous nucleation sites within the dentine collagen matrix, which promote and regulate the mineral precipitation processes. Indeed, it is well known that stabilised non-collagenous phosphoproteins are involved in biomineralisation procedures due to their high affinity to Ca^{2+}. It has been proposed that during nucleation, Ca ions are first adsorbed by the negative charges on phosphoproteins. The role of the phosphate in aiding nucleation of apatite on a biological surface can be played by existing phosphate ions adsorbed on the organism itself and more are present in the dentine substrate that is conditioned with EDTA and mild self-etching adhesives, providing more phosphate to enhance apatite formation. Calcium phosphate minerals are often identified based on their calcium/phosphate ratio, and the mineral component of dentine has been found to have a ratio of ~1.49:1.

Maintenance of inorganic phosphate homeostasis is essential for normal tooth development, maintenance and repair. At low tissue fluid phosphate concentration, calcium pyrophosphate-dehydrated crystal formation is partially inhibited by the phosphate. At high phosphate concentration, calcium pyrophosphate, calcium phosphate and unstable and non-crystalline amorphous calcium pyrophosphate-phosphate complexes are formed. Conversely, inorganic pyrophosphate is a potent inhibitor of hydroxyapatite (HA) crystal growth. Non-specific tissue alkaline phosphatase, which is present at all mineralisation sites, can hydrolyze pyrophosphate; as a result, these two factors work in concert to control local levels of pyrophosphates whose local modulation might be a strategy to encourage dentine remineralisation.

This alkaline environment within the resin-dentine interface may interfere with the activity of matrix metalloproteinases (MMPs), which are acidic-pH dependent. The main function attributed to MMPs is the degradation of the dentine and bone extracellular matrix. However, it is now widely acknowledged that MMPs play an important role in signalling by generating peptides with specific biological activities. Dentine matrix protein 1 (DMP1) can be cleaved by MMP-2 (and other MMPs) to release a C-terminal telopeptide, which is potentially able to promote the differentiation of dental pulp stem cells. MMP-2 is a predominant protease in the dentine matrix with a large substrate specificity. The C-DMP1 fragment was suggested to be a nucleator as it is localised within mineralised matrices, whereas the N-DMP1 fragment is believed to be a mineralisation inhibitor as it is localised in unmineralised matrices. The C-DMP1 polypeptide induced cytodifferentiation of cells after trauma of tooth in a rat pulp injury model, as a dense and continuous reparative dentine bridge was observed within 2 weeks, suggesting accelerated pulp healing capacity. It is thus tempting to extrapolate that during the dentine adhesive procedure, cleavage of DMP1 by MMPs would be activated by the acid, leading to the release of active fragments which could promote remineralisation healing. Partial demineralisation of a mineralised collagen matrix by acids exposes the collagen scaffold to be remineralised, but also activates the proforms of dentine MMPs. Effective inhibitors of MMPs may protect the seed crystallite-sparse collagen fibrils of the scaffold from degradation before they could be remineralised.

New Advanced Materials at the Resin-Dentine Interface

Glass Ionomer Cements

Glass ionomer cements (GICs) have improved substantially since Wilson and Kent introduced these materials in the early 1970s. GICs are self-adhesive materials that bond to polar substrates and tooth hard tissues (bone, enamel, cementum and dentine) through combined micromechanical and/or chemical bonding, which is in contrast to composite resins that only bond micromechanically. In general, this chemical adhesion may be divided into two stages: the free COOH groups form hydrogen bonds with the substrate, and when the reaction progresses, the flexible hydrogen bonds are converted into stronger ionic bridges without undergoing great dimensional changes in a moist environment in response to a change in temperature [8].

Conventional GICs are dispensed in both powder forms with its liquid component. The powder is composed of fluoro-aluminosilicate glass; the liquid is an aqueous solution of a poly-alkenoic acid, such as polyacrylic acid. In detail, the first phase of the acid-base reaction that takes place after mixing both powder and liquid consists of a dissolution phase, where the acid (proton donor) attacks the surface of the glass particles (proton recipient) to release ions (aluminium, fluoride, and calcium or strontium). Then, the polyacid molecules become ionised, adopting a more linear form. This converts the carboxylic group of the polyacid and makes them more accessible for ions, promoting cross-linking in the later stage of gelation and thus forming a hard polysalt matrix. The resultant compound is formed by unreacted glass particle cores, immersed in siliceous gel and embedded in a poly-acid-salt matrix which binds the component together. The setting reaction may, as result, be summarised in four stages, i.e. decomposition of the powder, gelation, hardening and maturation. GICs are characterised not only by the fluoride release but also by the recharge capacity. GICs are widely used restorative materials with a preventive effect on caries. Fluoride released from GIC restorations inhibits the progression of initial proximal caries in adjacent teeth. There is significantly higher remineralisation of interproximal caries-like lesions adjacent to GIC restorations than adjacent to resin-based restorations, which indicates replenishing of the lost ions in the demineralised dentine. During demineralisation, GIC releases fluoride to the environment, and during remineralisation, fluoride is taken up by the dental substrate.

GICs can be placed in cavities without any need for bonding agents in order to be integrated into the dentine structure; they also have good biocompatibility. Dentine and GIC exchange ions once the cement is placed on the tissue. The cement leaches its ions as the glass is being dissolved by the polyacid; dentine, on the other hand, releases calcium and phosphate as a consequence of the self-conditioning effect of the setting cement on dentine. The new zone generated at the cement-dentine interface, as a product of the ion interchange, is called the intermediate layer.

The most important disadvantages of conventional GICs are the lack of sufficient strength and toughness and a short setting time; in addition, they attenuate moisture sensitivity. To offset this drawback, resin-modified GICs (RMGICs) have been introduced. The self-adhesiveness of RMGICs is attributed to ionic bonding to HA that remains attached to the partially exposed collagen fibrils, as well as to micromechanical interlocking for those RMGICs that additionally hybridise dentine. RMGICs are usually formulated from fluoro-aluminosilicate glasses, photo-initiators, polyacrylic acid, water and water-soluble methacrylate monomers, such as hydroxyethyl methacrylate, which may or may not be grafted onto the polyacrylic acid. As a result, RMGICs have the same ion-releasing glass as filler particles used in conventional GICs but in small sizes. In RMGICs,

light-activated polymerisation and free radicals of the hydroxyethyl methacrylate molecule have a role in setting, in addition to ionic cross-links between polyacrylic chains. RMGICs, on the other hand, and in spite of containing a small amount of a polymerisable monomer, will still undergo a true acid-base setting reaction. The quantity of the resin is limited (<5–10%) to the extent that it will not interfere with the normal acid-base setting reaction, allowing the ion exchange adhesion with the tooth structure that is typical of GICs [9].

Bio-activity can be defined as 'materials that elicit biological response at the interface between tissues and the material, which results in the formation of a bond' [8]. There is increasing interest in the use of bioactive materials in dentistry in an attempt to remineralise dentine. Some bioactive glasses (containing silicon, sodium, calcium and phosphorus oxides at specific weight percentages) have been added to the GIC structure to improve GIC bioactivity and tooth regeneration capacity, producing HA and forming of a strong bond between the collagen and HA. In order to improve the mechanical properties, bioactive glasses have been added to RMGICs, and it has been stated that the compressive strength of the composition decreases a little, but is still much higher compared with conventional GICs containing bioactive glasses, preserving the antimicrobial activity. These bioactive materials might be more effective in tooth restorations in open/close sandwich techniques or root surface restorations compared to RMGICs or conventional GICs, particularly in patients at high risk for caries.

Concerning the evolution of GICs, there has been some debate over the years as to whether all GIC-like materials are considered true GICs. Some of these GIC-like materials, such as polyacid-modified composite resins (wrongly called compomers), have been marketed as belonging to the GIC family. However, compomers resemble composite resins in their physical properties. They do contain ~30% resin, 30–35% polyacids

and water. Additionally, the acid-base reaction in compomers may be merely a temporary surface phenomenon, and the complete setting may not occur in the dark. 'Glass Carbomer', containing nanoglass particles of HA/fluorapatite, has been proposed as a new material development, but it produces reduced biomineralisation [8].

Calcium and Phosphate Cements, and Their Evolution

Mineral trioxide aggregate (MTA) has rapidly gained acceptance in dentistry since its introduction in 1993 by Torabinejad. MTA was developed and recommended initially for root end filling material and subsequently for pulp capping, pulpotomy for primary teeth, apical barrier formation for teeth with necrotic pulps and open apexes, apexogenesis, apical barrier formation in teeth with open apexes, repair of tooth perforations and as a root canal filling material. It is hard tissue conductive and inductive, and biocompatible [10].

The original formula of MTA developed from the first calcium silicate-based cements, which were based on Portland cement. Its composition was made of tricalcium silicate, dicalcium silicate, tricalcium aluminate (lastly, reduced) and tetracalcium aluminoferrite (lastly, eliminated). Next, calcium sulphate and bismuth oxide were added as radiopacifier for clinical control. Bismuth is present in both hydrated and non-hydrated MTA, and is also a part of calcium silicate hydrate. The primary difference between MTA and Portland cement is the lack of potassium and the presence of bismuth oxide. Additionally, a lower content of calcium dialuminate and calcium sulphate (unhydrated) is present in MTA than in Portland cement.

The calcium silicate hydrate comprises many amorphous calcium silicate hydrates that result from the hydration of tri- and dicalcium silicate phases, precipitates as a colloidal material and grows on the surface of unhydrated calcium silicate granules. This combination produces a

matrix that binds the other components together, gradually replacing the original granules. Calcium hydroxide occupies the water-filled spaces located in the components of the hydrating cement. The calcium hydroxide is the cause of the high alkalinity of MTA after hydration, creating an antibacterial environment; on the other hand, an acidic environment (EDTA and acid-etch procedures) exerts an adverse effect on some micromechanical properties of MTA as porosity increases; porosity and compressive strength could be influenced by the addition of various weight percentages of bismuth oxide.

Lowering the powder/liquid ratio might adversely affect those properties. MTA is one of the root end filling materials most resistant to bacteria and dye penetration [11]. MTA has also shown an optimal adaptation to tooth structure. Concerning biocompatibility, it is neither mutagenic nor neurotoxic, and does not produce a significant side effect on the microcirculation. On the contrary, the application of MTA promotes dental pulp cell differentiation, alkaline phosphatase activity, dentine sialophosphoprotein, bone sialoprotein and mineralisation. In this aspect, MTA has been confirmed to be an ideal pulpotomy agent in terms of dentine bridge formation which also preserves normal pulpal architecture via the release of different signalling molecules; in addition to this, MTA favours the differentiation and migration of hard tissue-producing cells. Moreover, only MTA may stimulate hard tissue deposition in direct contact with the root end filling material with the lowest periapical inflammation via modulation of cytokine production.

MTA is available in several forms and is presented as a very fine powder which is mixed with sterile or distilled water; both components are provided predosed for a predetermined water-powder mass ratio to be mixed on a sterilised glass slab for 30–60 s to obtain a 'sandy' consistency. According to the manufacturers, the working time is ~5 min (although this is said to be lengthened by covering the mixed material with moistened gauze to slow down evaporation, even though its setting is not by drying). MTA is a so-called hydraulic cement (i.e. sets and is stable under water), but the handling of MTA has been viewed as one of its shortcomings. Greater condensation pressure makes the material to become more compact with fewer microchannels; however, the reduced water uptake hinders complete MTA setting and results in decreased compressive strength and surface hardness. The microhardness decrease has been associated with the absence of the characteristic needle-like crystals. MTA lacks a short setting time; for this reason, it is important to place overlying permanent materials over MTA, which do not interfere with its setting properties. When MTA is used as a root canal filling material, some of its limitations should be taken into account, such as the difficulty in controlling the length of the filling, the chance of producing voids and the absence of a known solvent for MTA removal [10].

Clinically, GICs, which are placed over 45 min as opposed to 72 h for MTA, showed no effect on crazing, setting time or shear bond strength, but there was a noticeable formation of calcium salts at the interface. Filled resin and polyacid-modified resin composites may be placed over MTA after 48 h using conventional adhesive techniques.

Inductive Therapeutic Function with Doped Dental Adhesives

Dentine adhesives should not only be long lasting, but also promoters of both protection and remineralisation of resin-dentine interfaces, triggering the bioactive nature of dentine matrix by releasing bound bioactive molecules.

In order to favour ion exchange and mineral precipitation within the dentine-bonded interface, several doping compounds represented by some biologically active agents have been incorporated into dental adhesives to repair any nanometre-sized void that remains within the hybrid

layer after polymerisation of the adhesive. They are bioactive glass, Portland cement or amorphous calcium phosphate, but their essential elution leading to rapid decrease in mechanical properties and bond strength reduction make them controversial. Ceramic bioactive nanospheres, such as HA, have also been proposed as resin fillers, but they do not possess a controllable release and optimal degradation kinetics. Finally, calcium and phosphorous are able to stimulate tissue mineralisation but only at a certain concentration.

Zinc has been proposed as a doping agent in dental adhesives. Zn is a cofactor of many enzymes and is essential for DNA replication. It has a potent inhibitory effect on osteoblastic bone resorption and can modify the production of cytokines. Zinc ions inhibit MMPs and reduce collagen degradation in demineralised dentine [12]. Selectivity for a specific MMP may be a function of differences in Zn/Ca ratios. Zinc has been shown to promote binding between collagen and other oligomeric matrix proteins. Protein-protein interactions are controlled by the presence of metallic cations and probably dictated by the zinc ion as the preferential ligand. Multiple strategies have also been adopted in order to inhibit MMPs, such as the inclusion of a hydroxamic acid-containing polymer on microspheres, which preferentially bind the zinc in the active form of MMPs in the local tissue environment. Zinc also influences signalling pathways, stimulating a metabolic effect in hard tissue mineralisation and dental remineralisation processes [13]. Multiple actions have been planned by loading resins with bioactive components. The antibacterial effect of silver nanoparticles, remineralisation strategies by calcium phosphate nanoparticle inclusion, synthesis of multiple ion-releasing glass filler or addition of growth factors have even been postulated.

Zinc-doped adhesives may be obtained using 10% ZnO or 2% $ZnCl_2$ (composition by weight). Higher solubility of ZnO when in contact with acid substrates, as some acidic non-collagenous proteins (dentine matrix proteins), could also account for the effective release of zinc ions. Zn-loaded micro (~2.5 μm) and nanospheres (~350 nm) have also been synthesised and proposed for therapeutic purposes at the resin-dentine interface. They are composed of 2-hydroxyethyl methacrylate as a backbone monomer, ethylene glycol dimethacrylate as a cross-linker and methacrylic acid as a functional monomer. Zinc loading was promoted by immersion in ZnCl 0.1% (w/v) [pH 7.5] solution for 30 min. These particles are able to act as sequestering agents for Ca and P facilitating dentine remineralisation, supported by the presence of silicon, which in turn plays a role in the binding and incorporation of CaP to the collagen network. Silica nanospheres have been shown to mediate the formation of CaP precursors, which act as nucleating minerals.

Specific Zn-doped dentine adhesives, as a consequence, may have therapeutic/protective effects for stabilising the hybrid layer and inducing mineral precipitations within the resin-dentine interface, though it may be that the presence of Zn retards calcium compound crystallisation [14]. ZnO nanospheres have been shown to increase collagen synthesis and non-specific tissue alkaline phosphatase activity, interpreted as osteoblast differentiation and bone matrix maturation. The binding constant of Zn is 8.7 and that of calcium is 6.8; as a consequence, Zn can compete with Ca for binding pyrophosphate resulting in the formation of new crystalline complexes with less susceptibility to acid dissolution of these structures. The formula for stoichiometric HA is $Ca_{10}(PO_4)_6(OH)_2$. However, biological apatite is calcium deficient and contains substantial amounts of carbonate. Carbonated apatite is a precursor of HA, but when it is precipitated in the presence of zinc an exchange between Zn^{2+} and Ca^{2+} occurs in vitro forming a substituted apatite compound. An isomorphous substitution can be obtained when Ca^{2+} is replaced by Zn^{2+} into dentine HA. The radius of doped ions of Zn

(0.074 nm) is smaller than that of Ca (0.099 nm); thereby, it is easy for zinc to fill in the vacancy or interstitial sites of crystal lattice. These ions, in interstitial sites, force the crystal to lose certain electric charges, needed to maintain its electric neutrality. Analysis of X-ray diffraction spectra may reveal characteristic peaks of scholzite (zinc-substituted HA) – $[CaZn_2(PO_4)_2\ 2H_2O]$ [15]. This Zn-HA complex shows decreased crystallinity, which is inversely proportional to the Zn fraction increase, but higher bioactivity and osteoconductivity, and less solubility than HA when in contact with body fluids.

Conclusion

Acidic agents not only demineralise dentine, they also promote wettability by erosion of intertubular dentine and enlargement of dentinal tubules through peritubular dentine dissolution; which leads to a dentine decrease of surface energy due to exposure of collagen fibres and loss of mineral content. Etch-and-rinse adhesives normally use phosphoric acid or some milder conditioners (EDTA) for this purpose. EDTA causes dentinal erosion but removes less amount of calcium from the dentine surface, which promotes shallow demineralisation and induces favourable chemical modifications that improve dentine wettability and penetration of hydrophilic monomers. When EDTA is applied to dentine, the structural support of the collagen fibrils is not lost, explaining the better resistance to degradation of demineralised dentine and resin bonds to EDTA-treated dentine.

Dentine contains matrix-bonded bioactive molecules, enzymes and growth factors that may be liberated and activated through different mechanisms in order to complete reparative processes, even in the absence of cells. Collagen can direct the crystallisation process once it is infiltrated with some amorphous precursors in order to achieve hierarchical functionalised biomineralisation of the matrix. To promote a growth centre, the collagen structure should be sound in addition to the presence of residual mineral crystals; the presence of phosphoproteins is also recommended, and EDTA does not remove them from the dentine after partial demineralisation. In order to promote remineralisation healing, some inhibitors of MMPs should be considered in order to protect the seed crystallite-sparse collagen fibrils of the scaffold from degradation before they could be remineralised.

GICs are self-adhesive materials that bond to polar substrates and tooth hard tissues through combined micromechanical and/or chemical bonding. They set by an acid-base reaction. The setting reaction follows the successive stages of decomposition of the powder, gelation, hardening and maturation. GICs are characterised not only by the fluoride release but also by their recharge capacity. Their good biocompatibility is also remarkable. GICs may be modified with resin (5–10% RMGICs/30–35% polyacid-modified composite resin) and bioactive glasses for example.

MTA has also shown an optimal adaptation to the tooth structure and is a potent mineralising agent. Concerning biocompatibility, it is non-mutagenic, non-neurotoxic and does not produce a significant side effect on the microcirculation; on the contrary, the application of MTA promotes dental pulp cell differentiation, increases alkaline phosphatase activity and modulates cytokine production.

The production of cytokines may be modulated by zinc, which has been proposed as a doping agent in dental adhesives. Zinc ions inhibit MMPs and reduce collagen degradation in demineralised dentine. Zinc also influences signalling pathways, stimulating a metabolic effect in hard tissue mineralisation and dental remineralisation processes. Therefore, specific Zn-doped dentine adhesives may have therapeutic/protective effects for stabilizing the resin-dentine interdiffusion

zone, inducing mineral precipitations within the interface, e.g. scholzite.

Finally, it is recommended to point out future directions that can be drawn from the last conclusions:

(1) EDTA should be proposed as a commercial conditioning dentine agent based on its capability to preserve collagen and form new minerals.

(2) Natural reparative processes of partially demineralised dentine should be implemented via the handling of bioactive molecules, enzymes, phosphoproteins and/or their analogues.

(3) In vivo controlled studies with Zn-doped dental adhesives are required.

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