Contemporary Restorative Ion-Releasing Materials: Current status, Interfacial Properties and Operative Approaches

[This article is for the minimum intervention themed issue]

Paula Maciel Pires [1,7], Aline de Almeida Neves [1,2], Irina Mikhailovna Makeeva [3], Falk Schwendicke [4], Vicente Faus-Matoses [5], Kumiko Yoshihara[6], Avijit Banerjee [2], Salvatore Sauro [3, 7].

[1]. Department of Pediatric Dentistry and Orthodontics, Universidade Federal do Rio de Janeiro, Rio de Janeiro, BRAZIL.

[2]. Conservative & MI Dentistry, Faculty of Dental, Oral & Craniofacial Sciences, King's College London, UK.

[3]. Department of Therapeutic Dentistry, Sechenov University of Moscow, 119435 Moscow, RUSSIA.

[4]. Department for Operative and Preventive Dentistry, Charité Centre for Dental Medicine, Aßmannshauser Str 4-6, 14197, Berlin, GERMANY.

[5]. Department of Stomatology, Medicine and Dental School, University of Valencia, 46010 Valencia, SPAIN.

[6]. National Institute of Advanced Industrial Science and Technology (AIST), Health Research Institute, 2217-14 Hayashi-cho, Takamatsu 761-0395, Japan; Okayama University Hospital, Center for Innovative Clinical Medicine, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, JAPAN.

[7]. Dental Biomaterials, Preventive & Minimally Invasive Dentistry, Departamento de Odontologia, CEU Cardenal Herrera University, Alfara del Patriarca, Valencia, SPAIN.

ABSTRACT

Minimally invasive (MI) concepts in restorative dentistry in the year 2020 request from the practitioner, not only a scientifically supported rational for carious tissue removal/excavation and defect-oriented, biological cavity preparation, but also a deep understanding of how to ensure a biomechanically stable and durable restoration in different clinical situations by applying different restorative options. Bio-reactive materials play an increasingly relevant role, as they not only replace diseased or lost tissue but also optimise tissue mineral recovery (among other properties) when used in restorative and preventive dentistry. Indeed, this is of certain interest in MI restorative dentistry, especially in those cases where gap formation jeopardises the integrity of the margins along resin composite restorations, causing penetration of bacteria and eventually promoting the formation of secondary caries. Recently, the interest on whether ion-releasing materials may reduce such biofilm penetration into margin gaps and reduce such a risk for development and propagation of secondary caries is growing significantly among clinicians and scientists. The aim of this article was to explore mechanisms involved in the process that allow mineral deposition at the interface between such materials and dentine and describe how conventional “bioactive” restorative materials currently available on the market may beneficial treatments in MI Dentistry.

1. Introduction

Teeth are formed through a highly organised mineralisation process resulting in hierarchically arranged tissues, each one with specific properties.[1,2] They are composed of a combination of tissues with different embryologic origin and precise genetic regulation to result in a unique composition, size, shape and spatial distribution of minerals and organic components, comprising enamel, dentine, cementum and pulp.[3]

During a lifetime, teeth are exposed continuously to changing oral micro-environments with harsh conditions characterised by the presence of extrinsic and bacterial metabolic acids, while being required to perform optimally under variable and high masticatory loads. In combination, these are the fatigue-exposure factors that lead eventually to enamel and dentine breakdown.[4] In enamel, demineralisation induced by low pH can be counterbalanced when the biofilm fluid/acquired pellicle/saliva is super-saturated with calcium and phosphate ions.[5] In dentine, however, the higher organic content of this tissue and its complexity, including the collagen network, makes the process of mineral repair more complicated.[6]

Minimally invasive operative intervention approaches are focused on the sole removal of the diseased tissues and replacement by a biocompatible material. Contemporary interventions, driven by the advent of “therapeutic” bio-interactive materials should now be used to broaden the application of this concept, resulting in tissue replacement which is able to reduce the susceptibility of tooth mineral to dissolution and/or being able to recover its mechanical properties via remineralisation.

2. Loss & gain of mineral in enamel and dentine

The dental caries process is initiated by a drop in pH within the biofilm induced by specific metabolic activities of the organised bacteria.[7] Tooth remineralisation may be expected to occur to a certain extent in the presence of calcium-saturated saliva and fluoride upregulates this process. Although a complete full-lesion remineralisation is unlikely, it is often also not required for arresting the caries process.[8] Hence, most advances in bio-interactive dental restorative material technology have focused on dentine remineralisation or dentine protection/replacement, also because the overall longevity of restorations is still of some concern in cavity margin sites located on dentine.

As previously stated, dentine is a complex tissue composed of mineral and organic phases. Dentine remineralisation is an intricate and dynamic process that entails highly orchestrated interactions of several cellular and matrix components.[9] Essentially, it involves the renovation of an organic phase (type I collagen), and inorganic apatite, leading to intrafibrillar mineralisation of collagen.[10] However, both stages must be in synergistic connection in order to allow precise mineral precipitation both within the collagen intrafibrillar and interfibrillar spaces and a recovery of the mechanical properties of the dentine tissue.[11]

For many years, the role of collagen in dentine was underestimated; it had been first considered only a passive organic scaffold.[12,13] However, recent evidence suggests that both the structure and assembly of type I collagen are essential in order to act as an active template for mineralisation, guiding the crystal deposition in parallel arrays, with preferential growth in the axial direction in the spaces between fibrils.[14] Minimally invasive

dentistry aims to minimise the amount of tissue removal and the maximal preservation of non-denatured collagen, which can be still protected by a hydroxyapatite coating.[15]

3. Background on the current guidelines for carious tissue removal

An updated approach to carious tissue removal has been recently reviewed and discussed.[16] Clinicians are still prompted to excavate lesions when a mechanically resistant tooth-restoration complex is needed to restore the patient's function and/or aesthetics. However, the traditional management has been for many years the complete or near-complete removal of the entire carious tissue biomass, in the belief that this would stop the caries process (non-selective removal). More recently, an improved understanding of the patho-physiology of the caries process and clinical trial evidence on carious tissue removal methods have supported the contemporary alternatives of "prevention of extension" as opposed to "extension for prevention".[17] In selective carious tissue removal, for instance, carious issue is only completely removed in the periphery of a cavity, ensuring the stability and longevity of the restoration, while close to the pulp, affected and in some cases, infected carious tissue may well be retained and sealed under the restoration if this prevents pulp exposure.

As a result, the sealed dentine beneath restorations placed following such carious tissue removal concept will be a combination of sound/translucent dentine at the cavity periphery and affected/demineralised dentine at the base, adjacent to the pulp.[18] Although conventional dental adhesives may achieve statistically lower bond strengths when applied to such affected dentine as compared to a sound dentine substrate,[19] the real values are still within the clinically safe standards for dental adhesion. [20] Importantly, the

surface area of the cavity affected in that way is usually small compared with the overall surface of the whole cavity.

Moreover, different carious tissue removal methods result in different histological dentine substrates and morphology of the residual dentine.[21,22] In general, chemo-mechanical methods reach a compromise between minimally invasive tissue removal to protect the pulp [23,24] and an "adhesion-friendly" substrate to enable successful restoration placement and interfacial longevity.[25] Figure 1 shows the morphology of residual dentine surfaces after different carious tissue removal techniques.

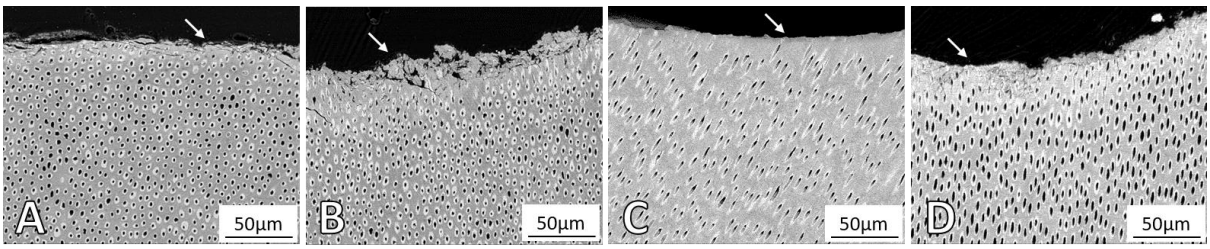

Figure 1: SEM images of carious dentine cavities after carious dentine tissue removal with a) conventional tungsten carbide burs; b) spoon hand excavator; c) Chemo-mechanical Papacárie (Fórmula & Ação, São Paulo, Brazil) (papain-based); d) Chemo-mechanical Brix 3000® (Brix Medical Sciences, Carcaraña, Argentina)(papain-based). Arrows point to the outermost excavated surface. Chemo-mechanical methods resulted in a relatively smooth dentine surface, with little dentine debris.

The use of conventional ion-releasing dental materials such as glass-ionomer cements (GICs) seems to provide a net mineral gain in carious dentine.[26] Using experimental biomimetic remineralising adhesive materials, it is possible to induce intrafibrillar mineralisation of collagen (Figure 2). Indeed, it has been demonstrated that such a biomimetic strategy for remineralisation may reinstate the mechanical properties of the demineralised dentine, as specific Ca/P compounds such as amorphous calcium phosphate (ACP), can fill the nanometre-sized spaces within the collagen fibrils.[26,27]

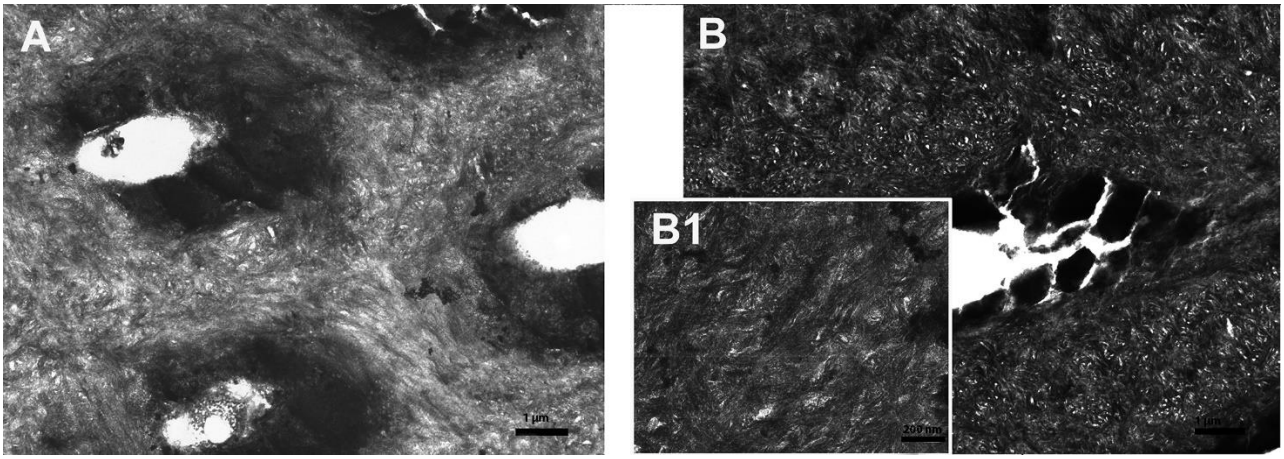

Figure 2. A: Transmission Electron Microscopy (TEM) assessment of demineralised dentine created with an in-vitro protocol to simulate caries affected-dentine. This image shows dentine collagen fibrils totally and partially demineralised. Images B and B1 (higher magnification of figure B) show the results obtained when such a substrate was treated using biomimetic analogues in combination with an experimental resin-based cement doped with fluoride-containing bioactive glass. In this case it is possible to see clearly a dentine with a total dark appearance resembling that of sound dentine, and indicating both intrafibrillar and extrafibrillar remineralisation.[26]

4. The role of new materials in engineering demineralised dentine

Polymer, ceramics or resin composite biomaterials can be used to repair or replace damaged organs or tissues in the human body. Research currently has focused on developing nanoscale materials with biomimetic properties. In dentistry, the effect of these dentine-replacement materials is clinically relevant and represented by ion leaching/releasing from the bulk material and interaction with the underlying tissue. Furthermore, the application of such materials may provide feasible means to extend the longevity of material–dentine interface. For example, experimental adhesives containing calcium-silicate based, bio-interactive micro-fillers have been found promising to preserve the bond strength against ageing.[28]

Ultraconservative interventions aim to preserve the sound structure of the tooth as much as possible. However, the preparation of minimally invasive cavities must be also supported by therapeutic restorative techniques that induce protection of the material-dentine interface against hydrolytic or enzymatic degradation processes, avoiding deterioration of the bond and failure of the restoration over time.[29] This concept of removal is accomplished by leaving partial or demineralised caries-affected dentine as a residual substrate. As mentioned before, it is known that adhesion to this type of substrate is compromised compared to sound dentine. This is probably due to a combination of the reduced biomechanical properties of caries-affected tissue (e.g., its modulus of elasticity) and the fact that the chemistry and structure of caries-affected dentine can affect the depth of dentine demineralisation and degree of adhesive infiltration.[30] Furthermore, irregular distribution and shallow penetration of adhesive monomers into demineralised collagen result in poor infiltration and adhesive phase separation. This hinders hybrid layer formation and results in a reduced bond strengths.[31] In order to improve the durability of the bond between adhesives and caries-affected dentine, alternative restorative procedures are necessary, most of them involving biomimetic (phosphoprotein) analogues.[32]

With improved understanding of this interaction between dentine and such bio-interactive “smart” materials, it may be possible to develop routes for the synthesis of new functional materials with structural precision at different dimensional levels. The ultimate goal is to produce materials to replace or protect the exposed collagen, mimicking as best as possible, the original sound tissue. Moreover, it would be interesting to investigate the possibility of extending their bio-interactivity by combining calcium phosphate (CaP)

phases with different solubilities and/or developing controlled release approaches to expand their use in caries prevention.

5. Conventional “bio-interactive” ion-releasing materials

Minimally invasive operative dentistry concepts require, as part of restorative therapy, materials which are able to: 1) deliver mineral ions; 2) bind to collagen (acting as template of calcium and phosphorus and stimulate nucleation of apatite crystallisation); 3) protect collagen from degradation; 4) provide an adequate pH to inhibit collagenolytic enzymes and 5) favour new mineral formation and 6) repel or constrain bacteria.[33] Ionic dissolution from ion-releasing materials may be the key factor in understanding their remineralisation potential. Calcium and phosphorous are the main components of the biological apatite. Other inorganic ions, such as fluoride, zinc, magnesium and silanol groups, may also act as substitutes in apatite crystal formation.

One description of “bioactive / bio-interactive” materials postulates that these materials should be able to elicit a specific biological response at the interface, resulting in the formation of a bond between the tissue and the material.[34] Part of the interaction mechanism is due to ion release and in this regard, some attention will be given to its laboratory and clinical properties applied to minimal invasive operative dentistry.

There are several materials already present on the market, which are able to release specific ions at the interface (Table 1). However, new “smart” materials are being developed to facilitate dentine remineralisation, incorporating inorganic fillers (bioglass, calcium phosphate, calcium silicate particles hydroxyapatite and silicon nanoparticles) in order to promote remineralisation at the bonded interface.[19,33] Although few of them cause

full remineralisation, they play an important therapeutic role at the interface. Table 1 offers an overview of current commercially available bio-interactive restorative materials.

5.1. Zinc polycarboxylate cements (ZPC)

Zinc polycarboxylate were the first dental cements showing some chemical adhesion to tooth structure. They were often used for luting restorations, intra-canal posts or orthodontic bands. It soon became clear that the use of zinc polycarboxylate resulted in more retention and less demineralisation in enamel under the bands compared to zinc phosphate cements.[35] The powder contains oxides of zinc, magnesium, tin, bismuth and/or alumina. Zinc and magnesium may act as a direct activator of the enzyme alkaline phosphatase and has been shown to inhibit osteoclast activity, so inducing the precipitation of poorly crystalized apatite.[36,37] Zinc is also known to induce collagen crosslink formation and may help to prevent enzymatic degradation.[38] The liquid is an aqueous solution of polyacrylic acid (PAA), a known non-collagenous protein surrogate for biomimetic intrafibrillar mineralisation of collagen fibrils[32] able to regulate the growth of the mineral crystallites during remineralisation processes. Indeed, this polymer has acidic characteristics and a predisposition to bind cations and stabilised amorphous calcium phosphate nanoprecursors.[39]

A recent study has shown the potential of these “traditional” cements in increasing the mineral density in artificially-induced carious dentine produced by a microbial protocol up to similar values achieved by GICs and calcium silicate cements.[40] ZPC in fact, have indeed slightly outperformed GICs in this regard (Figure 3). Figure 4 illustrates the high contrast outer layer formed over the ZPC restored samples after 45 days of intra-pulpal pressure with simulated body fluid (SBF). In modern dentistry, such materials would be

useful as pulp protection materials and/or as dentine replacement materials after deep selective carious tissue removal.

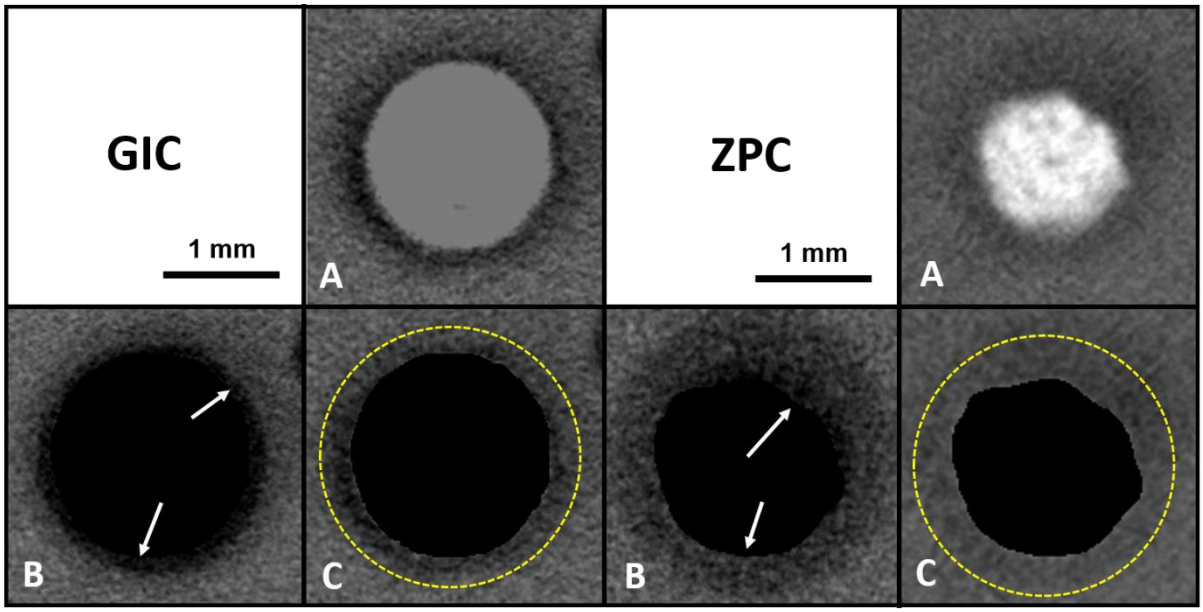

Figure 3: a) Micro-CT slices of glass-ionomer cement (GIC) or zinc polycarboxylate (ZPC) treated carious dentine cavities. b) Initial dentine caries cavity. Arrows point to carious dentine. c) Same region of the carious cavity after 45 days restoration with the experimental cement under simulated pulp pressure conditions (restorative cement is removed manually not to interfere with density evaluation). Although both materials were able to increase the carious dentine density (yellow dashed circle) after the period, ZPC showed a 19% higher increase in density values compared to the GIC sample (unpublished data).

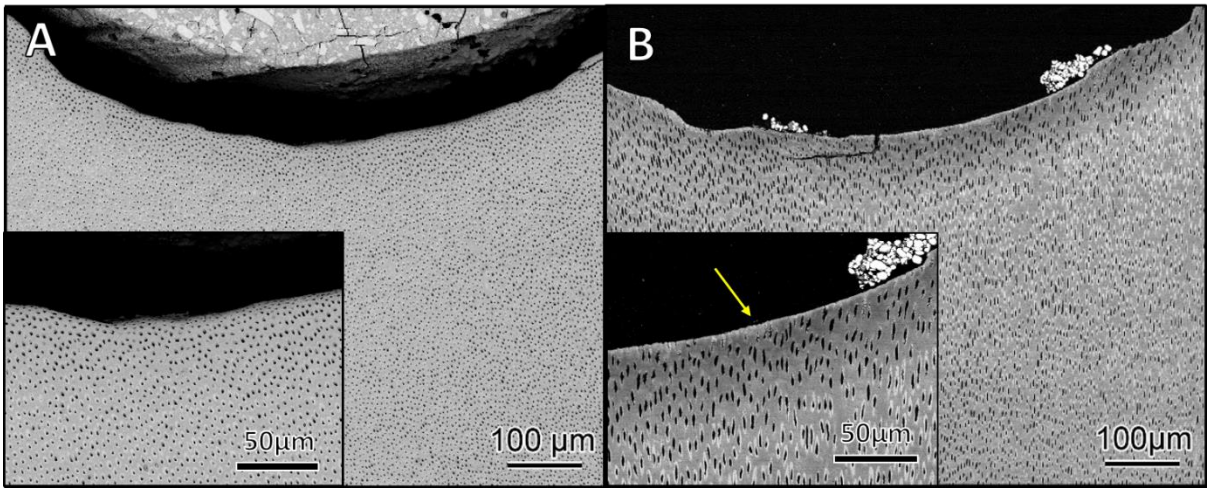

Figure 4: Scanning Electron Microscopy (SEM) images of dentine carious cavities restored with either GIC or ZPC after 45 days of intra-pulpal pressure with simulated body fluid (SBF). a) GIC restored carious interface. B) ZPC cement restored interface. For ZPC restored cavities, a high contrast outermost surface layer is detected (yellow arrow), indicating an increase of mineral density probably due to the interaction of dentine and the minerals released by ZPC.

5.2 Glass-ionomer cements (GICs)

Zinc polycarboxylate cements were clinically replaced by GICs, which also contain PAA but, in addition, also exhibit fluoride release. They are water-based restorative materials composed of fluoro-alumino silicate powder which, by acid attack, forms polyalkenoate salts that interact with the subjacent dentine forming an ion-interchange layer or diffusion zone. The formation of calcium polycarboxylate not only facilitates tissue remineralisation but also allows chemical bonding[41] at the interface. At the clinical level, this is a significant factor in the long-term adhesion and mineralisation ability, upgrading GICs as one of the most used restorative materials in paediatric dentistry, for example.

Modified forms of glass-ionomers, such as Glass Carbomers® have appeared on the market, with a similar composition and setting reaction to conventional GICs.[42] They are claimed to contain nanocrystals of calcium fluorapatite (FAp) and hydroxyapatite (HAp), which can act as nuclei for the remineralisation process and initiate the formation of FAp.[43] While they show reduced clinical success as a restorative material,[44] its use as a sealant or as pulp protection could be promising.

Resin-modified glass-ionomers (RMGICs) possess improved clinical properties. They are also considered self-adhesive materials and contain methacrylate-based monomers (HEMA, TEGDMA, UDMA), vinyl-modified polyalkenoic acid (VPA), photo-activators such as camphoroquinone and tertiary amines co-initiators, in order to allow

photopolymerisation.[45] RMGICs can bond micromechanically to dentine due to the resin infiltration of exposed collagen after PAA conditioning. They are also able to bond chemically to dentine by ionic interaction of carboxyl groups from the acid with calcium ions of the remaining hydroxyapatite crystals in the tooth substrate.[46]

The longevity of resin–dentine bonds may also be improved by using materials or clinical measures that may reduce the stress concentration at the interface between resin and dentine during light-curing procedures.[47] Resin-modified glass-ionomer cements (RMGIC) can be used in deeper cavities in order to provide a “stress-absorption” layer that will absorb part of the shrinkage of the resin composite used for the restoration.[48,49] This has been advocated to prevent stress development at the dentine-bonded interface[50,51] so decreasing the risk for gap formation and microleakage.

One more factor to consider as a source of degradation is the occlusal stress during mastication and in cases of parafunctional habits; all these factors can affect the integrity of the bond interface.[52] It has been shown that the use of RMGICs can provide a more stable bond to dentine, as well as provide a longer-lasting marginal sealing compared to resin composites. This seems to be correlated to the ability of such materials to dissipate the occlusal stress and to the beneficial result of the ions released over time. Indeed, it is of particular interest in modern, minimally invasive therapeutic restorative dentistry since it has been demonstrated that cyclic mechanical stress can promote gap formation at the margins of resin composite restorations. Bacterial penetration into narrow margin gaps might ultimately promote secondary caries formation.[53]

From RMGICs, other material classes have been developed. Giomers, for example, are resin composite materials where a pre-reacted glass-ionomer (PRG) filler technology has

been incorporated.[54] The main advantage of this material would be its improved fluoride release, but otherwise their clinical performance can be compared to conventional resin composites.[55] More recently, a new type of bioactive flowable resin-based restorative GIC, containing fluoro-alumino silicate particles and polyacid components, along with a bioactive ionic resin matrix has been developed (Activa™, Pulpdent, USA). One study[56] has demonstrated that the use of a conventional resin-modified GIC or the Activa™ restorative GIC/resin-based material can reduce the degradation during load cycling and/or prolonged storage in artificial saliva of the hybrid layer created with modern universal adhesive applied in etch and rinse mode (Figure 5).

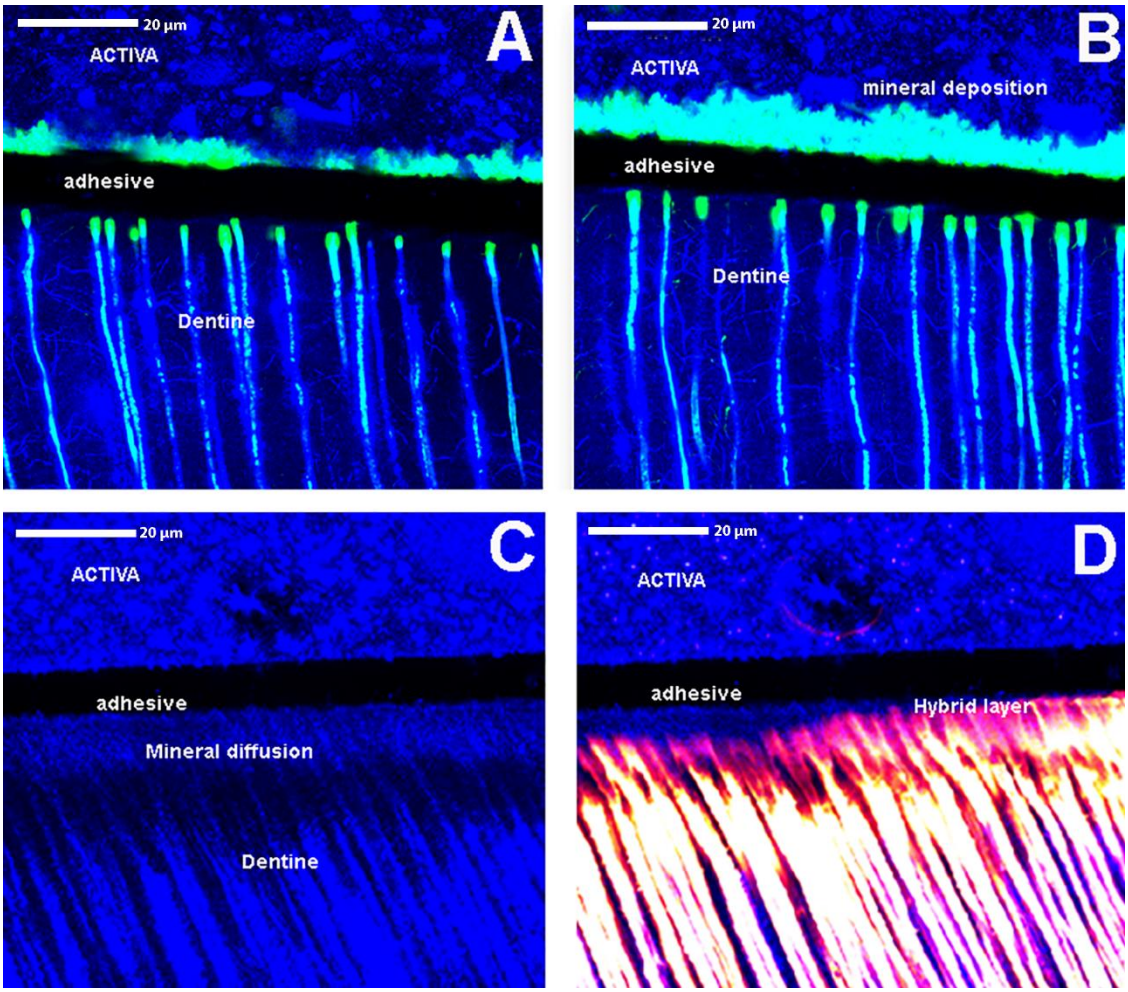

Figure 5: Confocal reflection/fluorescence single projection images of bonding interfaces created using universal bonding systems in combination with Activa™ restorative. In images A and B it is possible to see the interface created with the universal adhesive (Scotchbond™3M Oral care, MN, USA) applied in self-etching mode before and after load cycling and storage in artificial saliva, respectively. It is possible to recognise the increased presence of a porous reactive zone characterised by mineral deposition between the interface with Activa™. In images C and D an interface created with the universal adhesive (Scotchbond™3M Oral care, MN, USA) applied in etch & rinse mode before and after load cycling and storage in artificial saliva, respectively. In this case it is possible to note that the porosities within the hybrid layer are clearly reduced (nanoleakage in image D) by mineral precipitation (reflective signal in image C).

5.3 Bioactive glasses

Among other known bioactive and ion-releasing materials are bioactive glasses (BAG, bioglass).[57] The basic components of bioactive glasses are calcium oxide, sodium, phosphorous and silica.[58] The surface reaction is a complex, multistage process derived from their reactions with tissue fluids, which results in the formation of a biologically active hydroxy-carbonate apatite (HCA) layer.[59] It has been found that this reaction releases critical concentrations of soluble Si, Ca, P and N ions, which induce intracellular and extracellular responses.[60] Although most information about this material has been acquired through bone research, this material has been used in dentistry especially for dentine mineralisation[61] and for the treatment of dentine hypersensitivity.[62] However, the most common way to use bioactive glasses in dentistry is via air-abrasion/polishing procedures. Indeed, the pre-treatment of dental substrates using Bioglass 45S5® (Sylc, Velopex, London UK) in air-abrasion devices is currently used in restorative dentistry to create a “bioactive smear layer” within the interface, which can be incorporated into the hybrid layer within during application of RMGIC and self-etch adhesives. This bioactive smear layer remains available at the bonding interface and induce remineralisation and protection of the dentine-bonded interface.[19]

Moreover, it has been demonstrated that CaP has the ability to mediate matrix metalloproteinase-2 and -9 by forming a high molecular weight aggregate, CaP-MMP, that immobilise MMPs by binding to fibrin.[63] The binding capacity can also be influenced by the alkaline pH generated by the bioactive glasses during water immersion. A reduction in this activity is expected at pH around 10, since the ideal activity of MMP occurs at neutral pH. In addition, the surface created by Bioglass 45S5® is a SiO_2-rich gel layer.[36,64] The sequestration of calcium and phosphate ions from the glass and their diffusion through the SiO_2-rich layer can induce their transformation into amorphous calcium phosphates. After that, hydroxyapatite can be formed and it is well known that they may inhibit MMP activity.[65] The interactions between CaP complexes and amino acids indicates an involvement in bone mineralisation regulation. Although few studies focus on amino acids bound to surfaces, this appears to be due to an affinity of exposed collagen for the glass surface and chemical interaction between the dentine and glass, likewise in bone regeneration leading to apatite formation at the interface.[66]

5.4 Calcium silicate cements

The first calcium silicate dental cement, mineral trioxide aggregate (MTA), was developed in the 1990s as a repair material for endodontic perforations and root-end fillings due its biocompatibility and ability to induce mineralised tissue formation.[67] This cement is primarily composed of di- and tricalcium silicate, tricalcium aluminate, tetracalcium aluminoferrite and bismuth oxide. Calcium silicate cements are hydrophilic materials that can tolerate humidity and release calcium and hydroxyl ions into surrounding fluids (saliva, blood, dentinal fluid). These materials set by a hydration and precipitation mechanism, the remineralisation mechanism differing due to the alkaline nature of these

materials. Degradation of collagen fibrils occurs and leads to the formation of a porous structure, which facilitates the penetration of high concentrations of calcium and carbonate ions, leading to increased mineralisation in this zone.[68] It is important to note that they cannot induce biomimetic remineralisation by re-establishing functional properties. Their ability is to induce mineral precipitation and induce formation of a reparative/osteo-dentine.

Its clinical indications have been expanded to include pulp capping procedures, pulpotomies or root apical barrier formation.[69] Due to its biocompatibility and sealing ability, they have become an important material to support the concept of minimally invasive dentistry. As mentioned before, the alkaline setting reaction of these cements can reduce MMP activity and also has beneficial antibacterial effects on caries-affected and infected dentine.[70,71] Studies also demonstrated optimal healing responses with dentine bridge formation in the pulp space[72,73,74], confirming the biocompatibility of calcium silicates cements. They also exhibit expansion and contraction properties similar to dentine which results in higher resistance to margin leakage and subsequent bacterial migration.[71] Despite some of such materials may be affected by colour change or potential staining, all these properties together facilitate its successful clinical use.

6. Future prospects – dentine interface biomineralisation

Two different models of in-vitro remineralisation can be found in the literature, classified as the top-down / classical and bottom-up / non-classical approaches. A major criticism in the classical approach is that it results in extrafibrillar remineralisation without remineralisation of the intrafibrillar components.[32] Therefore, in this approach, conventional remineralisation does not occur by spontaneous nucleation of mineral

matrix, but rather by the growth of residual apatite crystals in demineralised dentine. If there are only a few residual crystals, there is no remineralisation.[10] On the other hand, the bottom-up approach was suggested as an alternative and is independent from apatite crystallites that may have remained. This biomimetic remineralisation is driven by analogues, leading to hierarchical remineralisation of dentine,[75,32] resulting in a highly ordered intrafibrillar nanoapatite assembly.

Dentine biomineralisation occurring within the restorative interface could be accomplished following the bottom-up strategy, where the crystals and structures formed can incorporate organic macromolecules.[6,14] It is known that in demineralised dentine, the collagen intrafibrillar gap regions are spaces which hydroxyapatite mineral precursors occupy, eventually nucleate and hydroxyapatite crystal plates grow.[32] It is therefore important to have mineral reincorporation when the dentine is exposed to demineralisation (from erosion, caries or restorative procedures).

A mineral crystal is formed through a nucleation event in which a cation and anion pair bonds and create nuclei for crystal growth. Many biominerals are formed by an amorphous precursor pathway mediated by a non-collagenous protein. Several inorganic materials have been shown to be bio-interactive and able to deliver remineralising ions. Once such biomineralisation processes are better understood and their place in the minimally invasive operative approach is recognised, the interaction between materials and tooth surfaces, namely “bio-interactivity”, should also be considered in the longevity of the tooth-restoration complex.[6,76] Development of biomaterials able to catalyse remineralisation of incompletely resin-infiltrated collagen matrices created by resin adhesives will represent a great advance in dental care.

7. Conclusions

There are different methods available to perform carious tissue removal. The first important concept to consider is the type of substrate that these methods leave to be treated. Thereby, a good diagnosis and the planned treatment could act together with the "smart" materials to heal the tissue left behind. Hence, in minimally invasive dentistry, the "bio-interactivity" is important to create a therapeutic surface for adhesive procedures.

As current commercially aesthetic resin composite materials have no ability to remineralise the collagen network after acid demineralisation, ion-releasing materials need to be used in association. Unfortunately, they are also not able to immediately remineralise the remaining caries-affected dentine. However, they have specific therapeutic activities that could improve the protection of collagen fibrils until the remineralisation process occurs.

In general, glass-ionomer cements and RMGICs have a chemical ability to bond directly to dental tissues, along with an ability to release specific ions capable of inducing mineral precipitation at the interface. Quick-setting calcium silicate-based cements could be indicated for deeper cavities due to their ability to stimulate the pulp cells to produce a reparative dentine bridge and create a calcium carbonates and/or apatite-like crystallization layers along the interface. Moreover, they also possess antibacterial properties against eventual remaining microorganisms left after selective carious tissue removal, reducing the risk for secondary caries and improving the longevity of restorations.

Application of modern adhesive systems in combination with ion-releasing dentine-replacement materials may offer to practitioners the possibility to perform adhesive

restorations with long-lasting performance. Furthermore, understanding the ion releasing process of materials may by the key factor for the development of a therapeutic bonding system, being a promising alternative way to reduce the degradation of the resin-dentine interface.

Table 1. Commercially-available “bio-interactive” ion-releasing materials

Type of material	Brand	Manufacturer
Conventional Glass Ionomer Cements	IonoStar Plus	VOCO, Germany
	IonoFil Plus	
	Aqua Ionofil Plus	
	Ketac™ Universal	3M ESPE, St Paul, MN, USA
	Ketac™ Fil Plus	
	Riva Self Cure	SDI, Australia
	GC Fuji II®	GC, Tokyo, Japan
High-viscosity Glass Ionomer Cements	Fuji IX Fast®	GC, Tokyo, Japan
	Fuji IX GP®	
	Fuji IX Extra®	
	Chemfil Rock	Dentsply, Germany
	IonoStar Molar	VOCO, Germany
	Ionofil Molar	
	Ionofil Molar AC Quick	
	Ketac™ Molar	3M ESPE, St Paul, MN, USA
	Ketac™ Molar Quick	
Glass Hybrid Cements	Equia Forte Fil	GC, Tokyo, Japan
Resin-modified Glass Ionomer Cements (RMGIC)	Activa™	Pulpdent, USA
	Ionolux	VOCO, Germany
	Photac™ Fil Quick Aplicap	3M ESPE, St Paul, MN, USA
	Ketac™ Nano	
	Vitremer™	
	Riva Light Cure UV	SDI, Australia
	Fuji II LC®	GC, Tokyo, Japan
Metal Reinforced Glass Ionomer	Ketac™ Silver	3M ESPE, St Paul, MN, USA
	Riva Silver	SDI, Australia
Glass Carbomer	Glass Fill	GCP Dental, Netherlands
Giomer	Beautifil II	Shofu Dental Corporation, Japan
	Beautifil II Gingiva Shades	
	BeautiSealant	
Composite	Activa™ Presto	Pulpdent, USA

	Re-Gen™ Flowable Composite	Apex, USA
	Re-Gen™ Bulk Fill Composite	
Adhesive	Re-Gen™ Bioactive Adhesives	Apex, USA
Resin-modified Glass Ionomer Adhesive	Riva Bond	SDI, Australia
	Fuji Bond LC®	GC, Tokyo, Japan
Calcium silicate-based cements	Endo-PASS	DEI Italia, Italia
	Biodentine®	Septodont, France
	ProRoot MTA	Dentsply, USA
	Angelus MTA	Angelus, Brazil
	MTA Bio	
	BioAggregate®	Innovative BioCeramix
	RetroMTA	BioMTA, Republic of Korea
	MTA Plus	Avalon Biomed Inc., USA
	Neo MTA	
	Endosequence BC sealer	Brassler, USA
	Generex A	Dentsply, USA
Resin-modified MTA	TheraCal LC	Bisco, USA
	Poly Zinc +	Prevest Denpro, India
	G.C.R.	Acrostone, Egypt
Zinc Polycarboxylate Cement	Durelon™	3M ESPE, St Paul, MN, USA
	HY-Bond	SHOFU INC, Japan
	SQ-ZPC	Aescu Pharma Co., Hong Kong

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