Caries Progression and Prevention Strategies: Demineralization vs Remineralization' - A Review Article

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Abstract

Dental caries involves interactions between the tooth structure, the microbial biofilm formed on the tooth surface and sugars, as well as salivary and genetic influences. The dynamic caries process consists of quickly alternating phases of tooth demineralization and remineralization, which culminates in the beginning of particular caries lesions at certain anatomical predilection spots on the teeth if net demineralization happens over a long period of time.

The remineralization process is a natural healing mechanism that returns minerals to the hydroxyapatite (HAP) crystal lattice in ionic form. The caries process is a continuous series of demineralization and remineralization cycles. We highlight and briefly discuss some of the most recent advancements in remineralization therapy in this article. Most modern medicines strive to boost fluoride's effectiveness by including additional potentially active substances such calcium, phosphate, stannous, xylitol, and arginine in the formulation. Other remineralization approaches have focused on forming remineralizing scaffolds inside the lesions (e.g., self-assembling peptides), while some innovative remineralization methods like use of lasers and biofilm modifiers etc., have made substantial development in recent years, the data for the majority of them is still insufficient to determine their genuine therapeutic value.

Keywords: Demineralization, Remineralization, Nanoparticles, Fluoride releasing agents, CPP-ACP, CPP-ACPF.

INTRODUCTION

Dental caries is a complex, dynamic disease caused by biofilms that causes phasic demineralization and remineralization of dental hard tissues. Caries can affect the tooth crown and, later in life, exposed root surfaces, and can develop in both primary and permanent dentitions. Caries start and development are influenced by the balance of pathogenic and protective factors. Pathological variables change the balance in the direction of dental caries and disease development, whereas protective factors promote remineralization and lesion arrest.[1,2]

The process of introducing minerals from the surrounding environment (saliva, biofilm) into partially demineralized tooth structures is known as dental remineralization. Remineralization can cause amorphous mineral precipitates in the intercrystal and interrod gaps, or it can replace minerals in partly demineralized enamel and dentin (Cochrane NJ, 2010). Remineralization might take either spontaneously or as a result of therapy. Fluoride – based treatments have the greatest degree of supporting evidence among the various therapies (Amaechi and van Loveren 2013; Fontana 2016), and widespread use of fluorides is often regarded as the primary cause of dental caries reduction in most populations. However, currently available F treatments have limited efficacy in some people, and the benefit of F in lowering dental caries prevalence has reached a plateau at the community level (Haugejorden and Magne Birkeland 2006). As a result, researchers have been working on novel remineralization treatments to bridge the efficacy gap. The majority of novel techniques have been developed to complement rather than replace established F therapies, although those that do not use F might offer an alternative for patients who are hesitant to utilise F.[3]

Remineralizing treatments now include the following:

1. Mineral saturation-increasing compounds, such as fluorides, CPP-ACP, CPP-ACPF, TCP, CSP; bioactive glass containing Calcium Sodium Phosphosilicate (Novamin), Sodium Trimetaphosphate
2. Biofilm modifiers, such as arginine, triclosan, and xylitol, as well as herbal substances.[4]

The pathophysiology of dental caries, as well as some of the most recent breakthroughs in remineralization therapy have been considered and reviewed in this article.

Pathophysiology of dental caries

Carious lesion dynamics are dependent predominantly on the availability of fermentable sugars, other environmental conditions, bacteria, and host factors. Specific environmental circumstances, such as the availability of fermentable dietary carbohydrates and the absence of oxygen, function as boosters for microbial activity. According to Reisine S, Litt M, a current perspective of caries involves consideration of how behavioural, social, and psychological variables, as well as biological elements, are involved. According to Nigel B. Pitts et al., dental caries is best defined as a complicated biofilm-mediated illness caused by frequent eating of fermentable carbohydrate (sugars such as glucose, fructose, sucrose, and maltose) and poor oral hygiene in conjunction with insufficient fluoride exposure.

Every cavity may have its unique demineralizing consortium of active organisms and genes when taken together, however the following basic principles are universal:

1) The presence of acidogenic-aciduric microorganisms, as well as their capacity to bind to the pellicle-coated tooth surface, either directly (as pioneered by MS) or indirectly (beneficiaries such as bifidobacteria and lactobacilli)
2) Conditions that favour the growth and metabolism of such species, including as availability to low-molecular carbohydrates, particularly sucrose, and a low redox potential. Fermentation and acid generation are accelerated when sugar levels are high and oxygen levels are low.

The resting pH of saliva tends to predict the caries experience of the individual and also is an indicator of salivary buffering capacity. Individuals with a resting salivary pH of around 7.0 had little caries activity or none at all, whereas those with a resting pH of 5.5 have a lot of caries. Caries activity is less severe in those with pH levels between 5.5 and 7.0. When subjected to a refined carbohydrate challenge, a lower resting salivary pH value predicts a noticeably low pH and the preservation of this low pH for a longer amount of time before recovering to the baseline resting pH level.[5]

The caries process is slow, requiring repeated episodes of prolonged acidic exposure persistently below the essential pH for enamel disintegration (pH 5.5, demineralization) with periods of restoration to the plaque's resting pH. (pH 7.0, remineralization period). The dynamic equilibrium between demineralization and remineralization will be tipped towards demineralization with the development of clinically detectable white spot lesions in the face of failure to remove plaque from retentive tooth areas, a diet high in refined carbohydrates, and frequent carbohydrate ingestion.

Prevention strategies of demineralization

Demineralization is the removal of minerals ions from hard tissue HA crystals such as enamel, dentin, cementum, and bone. Remineralization is the process of returning these mineral ions to the HA crystals. Because demineralization is a reversible process, partly demineralized HA crystals in teeth can remineralize if exposed to oral conditions that promote remineralization. The recent rise in the frequency of dental caries among young children has emphasised the need for a novel strategy to caries prevention in children under the age of six. Children should visit the dentist for the first time at the age of one or when their first tooth erupts, according to new disease preventive management models.[6]

Since the pathogenesis of dental caries is well understood, strategies to prevent caries development would seem to be relatively simple. Either the attacking forces can be reduced (dental plaque/dental biofilm removal, alteration of dental plaque so that it is less able to convert dietary sugars to acids, neutralisation of acids within plaque, removal or reduction of dietary sugars) or the host resistance can be enhanced (reduce enamel's solubility in acid, the potential for remineralization of demineralized enamel, covering enamel surfaces to create a barrier between dental plaque and enamel).[7]

Fluoride (since 1990), a well-known anti-caries agent, has demonstrated its potential to promote remineralization while inhibiting demineralization. Overexposure to fluoride, however, has been linked to the development of fluorosis. Although it is commonly established that fluoride is safe for the average person when used appropriately, it has been proposed that fluoride exposure be limited to specific individuals. As a result, various anti-caries measures are being developed.[8]

Professional application of fluoride has a long history. The benefits include the low frequency of applications (two to four per year) and the knowledge that the application has been completed. The cost is significant since professional time is consumed, and effort is required to attend the appointment. As a result, professional fluoride treatments are usually directed towards people who are most in need.[9,10]

Caries Management Tools for The Future

Several technical breakthroughs are on the verge of becoming clinical realities, and if they prove to be effective, they will be adopted.

Assessment of bacterial challenge by chairside molecular probes.

Caries risk assessment will require the use of chairside bacterial probes to determine a patient's cariogenic bacterial challenge.[11]

Caries immunization using dental caries vaccine**.** In the view of vaccine development, research focus is mainly on the incorporation of purified bacterial antigens into mucosal immune systems and delivery to mucosal IgA inductive sites. The three main types of S. mutans antigen that are involved in pathogenesis of dental caries and for which specific sIgAs have been found are antigen I/II, GTFs and glucan-binding proteins (GBPs). Accordingly, the mechanisms of action of these specific antibodies are:

- Clearance of bacteria in saliva by antibody-mediated aggregation,
- Inhibition of the adherence of bacteria by blocking bacterial-surface receptors and

Modification of metabolic functions of bacterial enzymes.[12]

Early caries detection and intervention

Early caries detection can be used to encourage remineralization by salivary augmentation, topical fluoride and chlorhexidine use, and diligent dental cleanliness. Furthermore, when new approaches for early caries intervention become available, many patients may no longer require restorations, maintaining tooth structure and preventing or reversing the course of dental caries.[13]

Caries prevention by laser treatment

The use of lasers in caries prevention was first encountered in 1972 by Stern and Sognnaes [15 diode lasers] using ruby Laser since then many investigations demonstrated the use of lasers in preventive dentistry and has been proposed that the lasers can be used as an adjunct to conventional fluoride therapy in remineralizing the tooth structure. The United States Food and Drug Administration (FDA) approved the use of an erbium: yttrium aluminum-garnet, or Er:YAG, laser on teeth in May 1997. This was the first time that a laser was approved for use on dental hard tissues. This FDA approval was for the use of this laser in the treatment of dental cavities and the cutting of healthy tissue prior to the implantation of restorations. For almost two decades, Kantorowitz and colleagues and Featherstone and colleagues have examined the impact of lasers on hard tissues. Fried and colleagues have released a study on a novel CO2 laser for removing carious tissue that is effective.[14]

Compounds Increasing Mineral Saturation

Numerous types of remineralizing agents and remineralizing techniques have been researched and many of them are being used clinically, with significantly predictable positive results.

Requirements of an ideal remineralization material are as follows:

- Diffuses into the subsurface or delivers calcium and phosphate into the subsurface
- Does not deliver an excess of calcium
- Does not favor calculus formation
- Works at an acidic pH
- Works in xerostomic patients
- Boosts the remineralizing properties of saliva[7]

Classification

Remineralizing agents have been broadly classified into the following:

- Fluorides
- Nonfluoride remineralizing agents
  - Alpha tricalcium phosphate (TCP) and beta TCP (β-TCP)
  - Amorphous calcium phosphate
  - CPP–ACP
  - Sodium calcium phosphosilicate (bioactive glass)
  - Xylitol
  - Dicalcium phosphate dehydrate (DCPD)
  - Nanoparticles for remineralization
    - Calcium fluoride nanoparticles
    - Calcium phosphate-based nanomaterials.
    - NanoHAP particles
    - ACP nanoparticles
    - Nanobioactive glass materials
- Polydopamine
- PA
- Oligopeptides
- Theobromine
- Arginine
- Self-assembling peptides
- Electric field-induced remineralization

The process of introducing minerals from the surrounding environment (saliva, biofilm) into partially demineralized tooth structures is known as dental remineralization. Remineralization can cause amorphous mineral precipitates in the intercrystal and interrod gaps, or it can replace minerals in partly demineralized enamel and dentin (Cochrane NJ et al. 2010). Remineralization might take either spontaneously or as a result of therapy. Fluoride – based treatments have the greatest degree of supporting evidence among the various therapies (Amaechi and van Loveren 2013; Fontana 2016), and widespread use of fluorides is often regarded as the primary cause of dental caries reduction in most populations. However, currently available F treatments have limited efficacy in some people, and the benefit of F in lowering dental caries prevalence has reached a plateau at the community level (Haugejorden and Magne Birkeland 2006). Consequently, investigators have been developing new remineralization therapies to close this gap in efficacy.

Calcium and phosphate are essential minerals for remineralization, while F plays a crucial role in enhancing the process. Because remineralization can be hampered by limited bioavailability of calcium and phosphate, new product formulations designed to ensure a constant supply of calcium and phosphate have been developed (Cochrane et al.

2010).[15] The following remineralization therapies were designed to directly increase mineral concentration in the environment around caries lesions (in saliva or biofilm).

Fluorides. For remineralization of caries lesions, F treatment is still the gold standard (Amaechi and van Loveren 2013; Fontana 2016). Various F treatments have been proved to be clinically beneficial in halting caries lesions, and F toothpastes have shown to have a dosage response (Walsh et al. 2010). Toothpastes with a fluoride content of 5000 ppm F are more effective in remineralizing root caries lesions than those with a fluoride content of 1000 to 1500 ppm F (Wierichs and Meyer-Lueckel 2015); nevertheless, evidence for their better effectiveness in remineralizing enamel lesions is still limited. As a result, they should not be recommended to all patients with active lesions, and their increased cost and restricted availability should also be considered.[16] F products at high concentration, such as varnishes, provide effective remineralizing therapy for noncavitated enamel lesions in primary and permanent dentition. Although F mouth rinses and high-concentration F gels have been demonstrated to be successful in reducing lesion development, there is little evidence that they can remineralize teeth. This paucity of data on remineralization may be due to previous research that concentrated mostly on F's caries-preventive qualities, which was the most common hypothesised mode of action at the time.[17]

Combination of some metals with F could enhance the antimicrobial effect of the therapy. Silver diamine F (SDF), for example, has been demonstrated to be very successful at remineralizing caries lesions in both coronal (Gao et al. 2016) and root surface (Wierichs and Meyer-Lueckel 2015) dentin. SDF has lately been investigated for its ability to remineralize early enamel lesions on the approximal and occlusal surfaces (MattosSilveira et al. 2014). Silver nitrate ($AgNO_3$) has been recommended as a replacement to SDF because it is not accessible in some regions. In a recent RCT, the effectiveness of 25% $AgNO_3$ followed by 5% NaF varnish in stopping early children caries lesions was compared (Chu et al. 2015). The most major disadvantage is that both SDF and $AgNO_3$ will colour the remineralized tissue black or dark brown.[10]

Stannous F (SnF_2), which has the ability to interfere with biofilm development while also affecting the demineralization/remineralization process, is another example of metal association with F that has rekindled interest in dental caries control. Tin ions have been shown to exhibit antibacterial properties in several laboratory investigations (partially reviewed by Fernández et al. 2016). In the presence of cariogenic biofilms, recent laboratory studies imply that current SnF_2 formulations have a superior anticariogenic impact (by inhibiting enamel demineralization).[18] The exact mechanism of action of SnF_2 is currently unknown. The most relevant calcium and phosphate–based systems accessible today are shown below.

CPP-ACP: Casein Phosphopeptide–Amorphous Calcium Phosphate (Recaldent). CPP-ACP is a calcium and phosphate-stabilized system that has been studied intensively over the past 20 years. Several literature and systematic reviews have been conducted on its anticaries impact (Azarpazhooh and Limeback 2008; Reynolds 2009; Zero 2009; Li et al. 2014). While the bulk of the studies indicated a significant remineralizing effect, the reviews expressed concerns about the lack of independent studies and the usage of short-term in situ models, which have limited practical applicability. Furthermore, the bulk of remineralization studies have been conducted on incipient lesions related with orthodontics, limiting the results' applicability to other areas. Other studies have recently shown that CPP-ACP remineralization may be achieved on non-orthodontic lesions ranging in severity from moderate to severe.[19] F varnish or a placebo were employed as the control in these 6-month studies. However, a 1-year clinical research found no advantage of CPP-ACP over placebo tooth mousse, most likely due to both study groups using daily F toothpaste. The conclusions indicated in recent studies (Li et al. 2014; Fontana 2016) are still valid due to inconsistent results, the short duration of the trials, and the dominance of solely fluorescence changes in lesions after orthodontics as the outcome. More clinical proof is still needed to demonstrate that the CPP-ACP therapy is not inferior to F therapies.[20]

CPP-ACPF: Casein Phosphopeptide–Amorphous Calcium Phosphate Fluoride. To improve remineralization effectiveness, F has been added to the CCP-ACP formulation. According to a recent systematic evaluation, this change in the formula has not been proved to be more beneficial than CPP-ACP alone. The most recent reports have produced mixed findings. CPP-ACPF did not give any further advantage in the remineralization of postorthodontic white-spot lesions, according to a recent study. CPP-ACPF was not proven to be more effective than conventional home care therapy in another short-term clinical research (Huang et al. 2013). CPP-ACPF appeared to have a particular remineralizing impact on smooth surface caries lesions but not on pit and fissure lesions, while another research found that CPP-ACPF was more effective than a placebo in treating pit and fissure lesions.[21]

fTCP: Functionalized β-Tricalcium Phosphate. TCP is a crystalline structure that has been functionalized to yield -tricalcium phosphate (fTCP). This fTCP was created to prevent calcium from reacting prematurely with ionic F, allowing it to function as a low-dose delivery mechanism (Karlinsey and Pfarrer 2012). There were no current clinical data on its remineralization potential that could be discovered. However, clinical trials including fTCP in varnish and high-concentration F toothpastes are now being conducted. CSPS stands for Calcium Sodium Phosphosilicate Bioactive Glass (NovaMin). Wefel (2009) and Burwell et al. (2009) reviewed the potential for this bioactive glass material for remineralization a few years ago, both stating that the technique was promising but that additional study was needed. RCTs were being conducted at the time the reviews were published. For this current review, no published clinical data were found for remineralization, and the level of evidence of in vitro and in situ data is weak and controversial. In vitro, NovaMin outperformed CPP-ACP mousse in boosting enamel remineralization, however in situ, adding 5% CSPS to sodium monofluorophosphate toothpaste did not increase remineralization of enamel specimens. TMP stands for Trimetaphosphate of Sodium. TMP is a cyclic polyphosphate salt that binds to the surface of the enamel. It was examined clinically in the 1990s and is presently being evaluated for its ability to boost the action of F. TMP addition of F varnishes (Manarelli et al. 2015) and gels (Danelon et al. 2013) leads to increased remineralization of simulated caries lesions, according to in situ data. Finally, TMP added to a toothpaste with a low F concentration demonstrated remineralization ability comparable to that of a toothpaste with a standard F concentration in situ. In situ data has clearly demonstrated the technology's promise; nevertheless, clinical application should only be recommended when these results have been verified in clinical trials. Overall, calcium phosphate–based systems have not consistently outperformed F products, and therefore should not be suggested to replace F products on a regular basis. Patients who are hesitant to use F products or young children who are at risk of dental fluorosis may benefit from calcium phosphate–based systems that are devoid of fluoride.[22]

Biofilm Modifiers

The following therapies were designed to enhance the remineralizing effect of F by affecting the amount, composition, and metabolic activity of the dental biofilm around caries lesions.

Arginine. The amino acid arginine has been proven in several investigations to impact the pH and ecology of dental biofilms. As a result, it was added to toothpaste (1.5 percent arginine) with insoluble calcium and 1,450 ppm F (as sodium monofluorophosphate) to help prevent cavities by increasing remineralization. This possible influence on biofilm pH might assist maintain biofilm equilibrium with the host, in addition to mechanical plaque management (Cummins 2016). Several randomised clinical investigations (5 for remineralization and 3 for caries lesions prevention) have shown that the arginine+F+Ca formulation has consistently superior effects when compared to nonarginine formulations. Three remineralization investigations were carried out in naturally occurring enamel caries lesions on the buccal surfaces of maxillary incisors, and the results were assessed using quantitative light-induced fluorescence (QLF; Srisilapanan et al. 2013; Yin, Hu, Fan). The other two trials (Hu et al. 2013; Souza et al. 2013) looked at the toothpaste's capacity to stop and reverse root caries lesions, using hardness as a clinical sign of lesion activity. According to a recent systematic review and meta-analysis, this formulation may have a better anticaries effect (Li et al. 2015). Because of the substantial risk of commercial bias in the research studied, a separate systematic review found that the current data is insufficient to establish the greater anticaries effectiveness of arginine-containing toothpaste.[23]

Triclosan. Triclosan is an antibiotic that may influence biofilm acid production, resulting in increased saturation and so remineralization. In the 1990s and 2000s, large studies revealed that adding triclosan to dentifrice formulations can result in small but statistically significant decreases in the incidence of coronal and root caries in children and adults. It was also indicated in a 2004 in situ research that it could have an influence on remineralization. triclosan-loaded dendrimers have recently been investigated as possible remineralization agents (Zhou et al. 2014), however no clinical data on this novel technology is now available.[24]

Xylitol. The use of chewing gum carrying xylitol increases salivary flow rate, helps in remineralization and enhances the protective properties of saliva. This is because the concentration of bicarbonate and phosphate is higher in stimulated saliva, and the resultant increase in plaque pH and salivary buffering capacity prevents demineralization of tooth surfaces.

Xylitol in oral syrups commercially available as: Mematrix Xylitol syrup.[25]

Herbal Compounds

In vitro studies of herbal or other natural chemicals as remineralization therapy have been conducted. They might impact mineral saturation and precipitation, operate as antimicrobials, or stabilize collagen, which could act as a scaffold for mineral deposition, depending on the component (Chandna et al. 2016). When remineralizing fake root caries lesions in vitro, proanthocyanidins have been found to have a synergistic impact with calcium phosphate–based drugs. While they appear to be a potential choice, more in situ and in vivo research is needed to corroborate the in vitro results.[26]

Self-assembling Peptides

Because minerals from saliva or other treatments require nucleation sites for precipitation and remineralization, a biomimetic technique was developed approximately a decade ago to speed up the process (Kirkham et al. 2007). In lab investigations, monomeric low-viscosity peptide solutions were shown to spontaneously generate scaffolds capable of hydroxyapatite nucleation, which facilitates remineralization in enamel lesions (Kirkham et al. 2007). Recent in vitro data confirmed the technology's remineralization capability, as evidenced by visual examination and scanning electron microscopy, QLF, photothermal radiometry and luminescence, microhardness, energy-dispersive x-ray spectroscopy analysis, and confocal laser scanning microscopy results. According to laboratory findings, the self-assembling peptide P11-4 diffuses deeply into the body of the caries lesion, enabling remineralization by promoting de novo hydroxyapatite nucleation (Kind et al. 2017). This treatment has been shown to be safe for human usage in a recent RCT (Alkilzy et al. 2017). The results of this 6-month single-blind trial show that P11-4 in conjunction with F varnish (22,600 ppm F) promotes remineralization of early carious lesions better than F varnish alone (Alkilzy et al. 2017).

CONCLUSION

In recent years, several remineralization methods have made substantial progress. The majority of these treatments work by establishing stable systems capable of delivering bioavailable calcium, phosphate, and F directly to the lesion or surrounding biofilm. One of the most difficult aspects of remineralizing treatments is providing the proper concentration of minerals at the right time; increased mineral concentration at the wrong moment might cause undesirable surface precipitation, reducing the therapy's efficacy. Mineral delivery that is slow and extended may promote subsurface mineral gain. Other treatments aim to change the environment around lesions (for example, biofilm modifiers) or the shape of the lesions' body (e.g., scaffolds). Finally, during the 2017 ICNARA meeting, a novel iontophoresis device developed to expedite the flow of mineral ions into deeper regions of demineralized enamel was introduced (International Conference on Novel Anticaries and Remineralizing Agents). Early results have been promising (Pitts 2017), although it is still too early to assess its remineralization potential.

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