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Role of remineralizing agents in pediatric dentistry– Review

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Abstract

Dental caries is a highly prevalent multifactorial and infectious oral disease known tp cause to significant public health problem for many centuries. The aim of modern dentistry is to manage non- cavitated caries lesion non-invasively through mineralization in an attempt to prevent disease progression and improve esthetics, strength and functions. The preventive approach of identification, the conservation of tooth structure, non-restorative of incipient caries serves both dental manpower as well as expense and suffering for the patient. The early diagnosis of incipient lesion can lead to new era in preventive dentistry as remineralization. So, the ultimate goal of treatment for caries management is use of remineralizing products this article focuses on different types of remineralizing agent used in dentistry.

Keywords: remineralization, caries, non-fluoridated remineralizing agents, minimal invasive dentistry

Introduction

Teeth plays a vital role in our lives and it serves numerous function beyond mastication, inclusive of shaping the kinectics of phonation, breathing, retaining a patent airway and serving as a foundation for the vertical dimension of the face [1].Teeth are composed of enamel, pulp-dentin complex and cementum. In human teeth enamel is the hardest substance as it is the most highly mineralized tissue constituted by approximately 96% mineral, 4% organic material, and water content [2]. Dental caries is a complex multifactorial disease and has been a significant major health problem for many centuries [3]. Owing to its globally healthy prevalence, Dental caries is a pandemic disease affecting the teeth characterized initially by the dissolution of the mineral portion of the tooth progressing to localized destruction of the enamel and dentine, and followed ultimately by inflammation of the pulp and periapical tissue if left untreated. evenually leading to discomfort and pain [4].

Dental hard tissues are continuously undergoing cycle of demineralization and remineralization. A drop in pH of oral cavity results in demineralization which if continued lead to loss of minerals from tooth structure resulting in dental caries. The reversal can occur if pH rises resulting in deposition of calcium, phosphate and fluoride Over the past decade, scientists have been working on more conservative treatments and dentistry has seen a paradiagm shift from its traditional mechanical-based surgical model to a biological -based medical model.

The initial caries lesions are “white spot” lesions implies that there is a subsurface area to have a greater likelihood of regression (remineralization) compared with inactive lesion as they have a more porous surface layer that allows for better penetration of the ions required for remineralization [5]. Early diagnosis of incipient lesion can lead to new era in preventive dentistry in the form of remineralization. The ultimate treatment modality for caries management at initial stages is use of remineralizing products [6].

“Extension for prevention” has given way to the current paradigm of minimally invasive dentistry. Minimum intervention as the term refers to the principle of treatment in dentistry in which early intervention minimizes tooth destruction because the disease is diagnosed prior to the tooth destruction. Hence it is possible to remineralize the caries lesions. Modern dentistry aims to manage caries lesions non- invasively through remineralization in an attempt to prevent disease and to improve form, function, strength and esthetic of teeth [7].

Background

Since the 1980’s customary fluoride-based remineralisation was regarded as the benchmark for rendering carious lesions inactive, which was established by the several evidence-based literature [8]. This considerable decrease in caries experience in developed nations from the twentieth century was mainly accredited to extensive utilisation of fluoride products. High amounts of fluoride in dentifrices and systemic fluorides have shown signs of toxicity which later led to the development of nontoxic fluoride alternatives as effective remineralizing agents.

The use of casein phosphopeptides (CPPs) as an anticariogenic and anticalculus was first described by Reynolds in 1993 and then amorphous calcium phosphate (ACP)-filled methacrylate composites 1996 [9]. In 1999, Enamel on toothpaste based on ACP technology was commercially developed by Dr Tung [10]. Then, in 2003, sugar-free chewing gums and mouth rinses containing CPP–ACP were in use, which has shown to remineralize the subsurface enamel lesions [11].

Sodium calcium phosphosilicate (bioactive glass) ceramic material which can provide calcium, sodium, and phosphate ions to form a hydroxyl carbonate apatite (HCA) was introduced as a remineralizing agent as it can attach to the tooth surface and release ions for remineralization. A toothpaste named "NovaMin" was introduced by Dr Len Litkowsky and Dr Gary Hack based on this formulation. The recent researches on remineralization are on biomimetic remineralization materials which were initially put forward by Moradian in 2001 [12].

Fluoridated and Non-fluoridated agents can cause the remineralization of the carious lesion.

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 [4].

Classification

Remineralizing agents have been broadly classified into the following:

Fluorides

- Topical
- Systemic

Non fluoride remineralizing agent

- 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

Fluorides

Fluoride is the most important remineralising agent in the prevention of dental caries. Fluorides can exchange with hydroxyl group in the apatite crystal forming fluorapatite. The fluoride can enter void spaces on the apatite crystals. Fluorides can even contribute to remineralisation of early lesions and act as an antimicrobial agent against bacteria and inhibits enzyme which are essential for the growth and bacterial metabolism.

With more than 50 years of clinical success, fluoride serves as the gold standard agent for preventing tooth decay. Fluoride has both systemic and topical actions that are important in preventing dental caries. Systemically, fluoride acts on teeth before their eruption by being incorporated into the crystal structure of enamel and thus making this tissue more resistant to the caries process. In addition, fluoride limits the demineralization of enamel and promotes its remineralization into a stable crystal structure which is more caries resistant. Systemic fluoride therapy is most effective when it is initiated during the maturation of the primary and permanent teeth. The most common forms of systemic fluoride therapy include water fluoridation and dietary supplements.

Fluorides also act topically, (i.e., directly on erupted teeth), by promoting remineralization and, to a lesser degree, through antibacterial action. These topical effects are significant and exposure of the tooth surface to low, regular doses of fluoride may be as critical in preventing caries as is fluoride ingested during tooth formation. Topical fluorides generally fall into two categories: (a) self-applied – e.g. toothpaste and mouthrinse, and (b) professionally applied – e.g. solutions, gels, foams and varnish. Professionally applied fluoride varnish, gel and foam are high concentration fluoride vehicles which are applied by healthcare professionals intermittently for caries prevention. Their caries preventive effect is topical and although they should not be ingested, small amounts will inevitably be swallowed by patients

Why non-fluoride strategies?

- Fluoride is highly effective on smooth-surface caries its effect would seem to be more limited on pit and fissure caries.
- A high-fluoride strategy cannot be followed to avoid the potential for adverse effects (e.g., fluorosis) due to overexposure to fluoride.
- Although fluoride presents no problems when used properly, among certain parts of the world, there has been the suggestion that fluoride exposure should be limited [14].

Functionalised Tri calcium Phosphate

Functionalised tri-calcium phosphate (fTCP) is the end product resulting from blending E-tricalcium phosphate (E-TCP) with organic and/or inorganic moieties, such as carboxylic acids and surfactants. Functionalised tri-calcium phosphate has the capacity to deliver targeted and sustained fluoride, calcium and phosphate. Its manufacturer claims it has a protective fumaric acid barrier resulting from ball milling beta-tricalcium phosphate with sodium lauryl sulphate, which is said to prevent the unwanted reaction between the individual ions and help in the co-existence of calcium and fluoride ions during its storage. When the agent comes in contact with saliva, the protective barrier breaks, releasing the ions for effective tooth remineralization. The remineralised tooth tissue achieved with fTCP and fluoride is considered to be more acid resistant. fTCP is an agent that works in synergy with fluoride to create stronger, more acid-resistant mineral relative to fluoride, β-TCP, or fTCP alone‘. However, addition of fTCP does not seem to accelerate the kinetics of fluoride, but appears to improve uptake of ions [15].

Dicalcium Phosphate Dihydrate (DCPD)

DCPD is a predecessor for apatite that readily turns into fluorapatite in the presence of fluoride. In clinical studies have shown that inclusion of DCPD in a dentifrice increases the levels of free calcium ions in the plaque fluid, and these remain elevated for up to 12 hours after brushing, when compared to conventional silica dentifrices [14].

ACP

Amorphous calcium phosphate (ACP) is a non-stabilized form of calcium- and phosphate-based remineralization system. It is the initial solid phase that precipitates from a highly supersaturated calcium phosphate solution, and can convert readily to stable crystalline phases such as octacalcium phosphate or apatite products [14]. These precipitated products have been found to be unsteady, so they change rapidly to a steadier form-HA or Fluor hydroxyapatite. Prior to their conversion, these ions must be available temporarily for below the surface remineralization Enamelon™ technology is based on unstabilized calcium and phosphate salts with sodium fluoride. It has been shown to be superior to conventional fluoride dentifrice in preventing root surface caries in radiotherapy patients [16].

CPP-ACP

Casein phosphopeptide amorphous calcium phosphate nanocomplexes (CPP-ACP) is a technology based on ACP stabilized by casein phosphopeptides (CPP). CPP maintains calcium and phosphate ions in an amorphous and non-crystalline state. In this state, these ions can enter the tooth enamel thereby hindering demineralisation and favouring remineralisation by precipitation of these released ions on the body of incipient lesions GC Tooth Mousse Plus™ and MI Paste Plus™ are formulations of CPP–ACP with incorporated fluoride to a level of 900 ppm, where the fluorides give additive effects in reducing caries experience. It is available as toothpastes, chewing gum, lozenges, and mouth rinses [17].

Sodium Calcium Phosphosilicate (Bioactive Glass)

A bioactive material is defined as a material that stimulates a beneficial response from the body,
Particularly bonding to host bone tissue and to the formation of a calcium phosphate layer on a material surface. Bioactive glass material containing calcium, sodium, phosphate and silicate. They are active when exposed to body fluids and deposit calcium phosphate on the surface of the particles [17]. *In vitro* and *in vivo* studies have proven that BG particles can be deposited onto dentine surfaces and later occlude the dentinal tubules by inducing the formation of carbonated HAP-like materials [18].

Nano materials

Nanoparticles exhibit better ion releasing profiles than micro particles Nano-materials have been incorporated into restorative materials as inorganic filler particles, like composites to release calcium, phosphate, and fluoride ions for remineralization of dental hard tissues [19].

Calcium Fluoride Nanoparticles

It has been stated that nanoCaF2 enhances the collective exposure of fluoride in comparison to conventional glass ionomer cement because the CaF_2 nanoparticle (nano-CaF_2) has a 20-fold higher surface area compared with traditional glass ionomer cements [19].

Calcium Phosphate-Based Nano-Materials

Nanoparticles of HAP, TCP, and ACP are the primary originating factors of releasing tooth mineral ions, and they enhance the supersaturation state of apatite crystals in cavitated lesions.

Nano-HAP

Synthetic nano-hydroxyapatite (nHAP) is a biologically compatible and biologically active material exhibiting comparable morphological characteristics, structural form, as well as crystallinity similar to apatite crystals. Nanoparticles tightly adhere to the surface of enamel as well as with plaque fragments and bacterial byproducts, thereby modifying their degree of crystallinity. Li *et al*. have indicated that n-HAP particles with a size of 20 nm fits well with the dimensions of the Nano defects on the enamel surface caused by acidic erosion and the nanoparticles can strongly attach to the demineralized enamel surface and inhibit further acid attack [19].

ACP Nanoparticles

Sphere shaped molecules with a proportion of 40 – 100 nm. ACP nanoparticle are added to the composite resins, ionomer cements, and adhesives serve as sources of calcium and phosphate ions. Studies using *in situ* human caries model showed that nanoACP-containing nanocomposites prevented demineralization at the restoration–enamel margins, producing lesser enamel mineral loss compared with the control composite

Proanthocyanidins (PA)

Grape seed extract (GSE) consist of proanthocyanidins (PA) is a bioflavonoid have benzene-pyran-phenolic acid molecular nucleus. At pH 7.4 it form visually insoluble HA complexes when combined with a remineralizing solution. In a study, the collaborative effect of PA in mixture with CPP-ACP on remineralisation of root caries, Epasinghe *et al*. noticed a substantial mineralisation and rigidity in artificial root caries [20].

Xylitol

Xylitol is a five carbon non-fermentable sugar alcohol commonly derived from brich tree which has suggested reduces streptococcus mutans (MS) levels in plaque and saliva by inhibiting their processes of energy generation of polysaccharides, ultimately resulting in a futile energy consumption leading cell death [21].

Polydopamine

Dopamine’s oxidative polymerization in aqueous solution automatically forms polydopamine, simulate dopamine which exhibits a sturdy adhesive property to numerous substrates underneath moist conditions. In demineralized dentin, polydopamine coated in collagen fibers, remineralization was promoted, which indicates that polydopamine binding to collagen fiber act as a new nucleation site that will be good for HA crystal growth [22].

Theobromine

Theobromine (3,7–dimethylxanthines) is an alkaloid, found in cocoa (240 mg / cup) and chocolate (1.89 %), exhibits crystalline growth in the enamel, It conclude that theobromine, with inside the presence of calcium and phosphate forms hydroxyapatite crystallites of an enlarged size that harden the enamel thus making it less prone to acid attack [23]. Further *in vitro* studies also indicates that coco bean husk.
efficiently reduces mutans streptococci which shows less toxicity in contrast to fluoride.

Arginine bicarbonate

Arginine is a amino acid observed in salivary proteins, with particle of calcium carbonate molecules that bond to the surface of mineral. when the calcium carbonate dissolves slowly, the released calcium is to be had to remineralize the mineral at the same time as the release of carbonate may give a slight local pH rise [24].

Poly (Amido amine) Dendrimers

Poly (amidoamine) (PAMAM) dendrimers or artificial proteins that mimic the self-assembling behavior of amelogenins to make a similar structure *in vitro* and are used as an organic template to control the synthesis of HAP crystals. Synthetic PAMAM exhibited the organization, orientation, and mineral phase of intact enamel when mutated at carboxylic acid groups, and HAP nanorods showed close parallelism with the original prism. However, remineralization of enamel via polyamide amine dendrimers (PAMAM) is time consuming and their clinical utilisation may be unreasonable unless they are potentiated [25].

Electric field- Induced remineralization

Wu initiated this approach to remineralize the completely demineralized dentin collagen matrix and also to reduces the mineralization time, which it achieved within the absence of both calcium phosphates and their analogs with the help of electrophoresis [26].

Self - assembling peptides

New development in research have revealed that peptide treatment provides a combined effect of increased mineral gain and inhibition of mineral loss from the tooth. The beta sheet-forming peptides, P114, that selfassemble themselves to make three-dimensional scaffolds under defined environmental conditions have been shown to nucleate HAP. The anionic groups of the P114 side chains captivate Ca++ ions, inducing the precipitation of HAP in situ [27].

Biomimetic Remineralization

There has been a change in understanding from reparative towards regenerative biomineralisation, wherein biologically similar tissues replace diseased dental tissues Mature enamel's acellular property and its inability to resorb or remodel itself, unlike bone or dentine, makes regeneration challenging. However, demineralised dentin collagen is then backfilled with ACP nano precursor particles in fluid state which are balanced by noncollagenous proteins. These pre nucleation clumps (~ 1 nm) then agglomerate into greater (10 - 50 nm) ACP nanoparticles in fluid state, which penetrate intrafibrillar water sections of collagen fibres and undertake self-building to transform into a metastable crystalline phase. The stabilised crystals eventually combine into single apatite crystallites within the zone between the collagen molecules [28].

Conclusion

The management of dental caries must be of a preventive rather than just curative approach. Preventive dentistry is all about how we stop the carious process-remineralize the initial noncavitated white spots, alter the metabolism in plaque and control plaque itself. The emphasis currently is being given to new technologies for enamel remineralization which suggest the changes in the understanding of dental caries. Recent investigations have primarily focused on various calcium phosphate- based technologies which are designed to supplement and enhance fluoride's ability to restore teeth. Although many potential agents have been identified in various models, very few have been taken forward to full anti-caries testing inhumans. In the future, non-fluoride agents which modify the production of acid in plaque either anti- microbially, biochemically, or directly and emerge to have the most promisefor use in topical products and may prove to be effective anticaries systems. With these alternative remineralization strategies, we would be able to re-establish the health of oral tissues without being under the risk of fluoride toxicity if ingested at high levels, in particular in children.

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