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Remineralization of Tooth: A Literature Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Non-cavitated carious lesions are managed non-invasively through remineralization in an attempt to prevent disease progression, and to improve strength, esthetics, and function of teeth in the modern dentistry. The emphasis presently is being given to new technologies which suggest the changes in the understanding of dental caries, and most of them gave significant positive outcome regarding remineralisation when used clinically. The aim of this review article is to put a light on various available remineralizing agents along with some recently introduced agents.

Keywords: Caries; remineralisation; fluorides; non-fluoridated remineralizing agents.

1. INTRODUCTION

Dental caries is one of the most common oral diseases that affects 60-90% of schoolchildren [1]. Dental caries is a multifactorial disease that starts with microbiological shifts within the complex biofilm and is affected by salivary flow and composition, exposure to fluoride, consumption of dietary sugars, and by preventive behaviours (cleaning teeth) [2]. In the face of failure to remove plaque from retentive tooth areas, a diet high in refined carbohydrates, and

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frequent carbohydrate ingestion, the dynamic equilibrium between demineralization and remineralization will be tipped towards demineralization with the development of clinically detectable white spot lesions [3]. However, if the pH is higher than 4.5 and F is present, the biofilm fluid is supersaturated with respect to fluorapatite (FA) and there is reprecipitation of minerals in the enamel. As a consequence, the net demineralization is reduced [4].

The remineralization process is a natural repair mechanism to restore the minerals again, in ionic forms, to the hydroxyapatite (HAP) crystal lattice. The process of tooth remineralisation has been studied over many decades of research and has lead to the development of technologies that can promote enamel remineralisation or reduce enamel demineralisation thus giving potential oral health benefits [5]. “Numerous types of remineralizing agents and remineralizing techniques have been researched and many of them are being used clinically, with significantly predictable positive results [6].

2. METHODOLOGY

Articles from “Pubmed” were searched with the keywords Remineralization-demineralization, Casein derivatives, Fluoridated remineralisation agents, Non-fluoridated remineralizing agents. 80 articles discussing remineralizing agents were read and 33 most relevant articles were included in this paper.

3. DISCUSSION

F is present in dental biofilm in enamel remineralisation. once After the exposure to sugars has ceased, acids in the biofilm are converted to salts which increases the pH. Once the pH reaches 5.5 or higher, the biofilm fluid is supersaturated with respect to HA and FA. The lost Ca and P by enamel can be recovered more efficiently if the biofilm still contains F [4].

3.1 Ideal Requirements of A Remineralizing Agent [4]

- Calcium and phosphate delivered into the subsurface
- No excess of calcium should be delivered
- No calculus formation
- Able to work at acidic pH during a carious attack to stop demineralization
- Effective in xerostomic patients also, as it increases carious process due to reduced saliva.
- Increases the remineralizing properties of saliva.
- Should be able to show some benefits over fluoride.

3.2 Indications [4]

- An adjunct to preventive therapy in high-risk patients for reducing caries.
- Reduce dental erosion in patients with gastric reflux or other disorders.
- Reduces decalcification in orthodontic patients.
- To repair enamel involving white spot lesions.
- Used for fluorosis, for teeth whitening and to desensitize sensitive teeth.

3.3 Classification of Remineralising Agent [6]

Remineralizing agents have been classified as:

- Fluorides
- Non-fluoride 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

3.4 Fluoridated Remineralizing Agents

Fluoride enhances the mineral content of early carious lesions and increases the speed of remineralisation process, hence, enhances the

enamel remineralisation [7]. When enamel is exposed to ionic fluoride, it may result in the formation of either fluorhydroxyapatite or calcium fluoride [8].

$$Ca_{10}(PO_4)_6(OH)_2 + F^- + H^+ \rightarrow Ca_{10}(PO_4)_6(OH)F + H_2O.$$

After fluoride therapy, calcium fluoride act as a fluoride reservoir which is not readily soluble. There are several types and forms of fluoride agents used in dentistry [7].

1) Topically applied fluoride therapy: self-applied and professionally applied methods.

    - Self-applied fluoride involves fluoride toothpastes and mouthrinses.
    - Professionally applied products include fluoride gels, silver diamine fluoride, fluoride varnish, and fluoride-containing restorations and sealants, such as glass ionomer cement [9]. It is used to arrest dentine caries, to remineralise early enamel caries or white spot lesions [7].

2) Systemic fluorides include milk fluoridation, water fluoridation, fluoride tablets/ drops/lozenges and salt fluoridation.

3.5 Sodium Fluoride

The hydroxyapatite crystals in enamel reacts with sodium fluoride solution applied on to the tooth surfaces to form calcium fluoride which forms main end product of the reaction which further forms fluoridated hydroxyapatite. The hydroxyapatite thus formed increases the resistant of tooth surface against the caries attack by increasing the concentration of fluoride on enamel surface. Gao et al. showed that the effectiveness of 5% sodium fluoride varnish to remineralize incipient caries lesions [10].

3.6 Stannous Fluoride

Muhler et al. [1950] introduced 8% and 10% solution of stannous fluoride as a topical anticaries agent during the decade of 1950-1960 and beyond with the pH of 2.1. It was based on the fact that greater reduction in rate of acid dissolution was seen when powdered enamel was treated with SnF2. Some clinical trials showed a greater caries reduction was seen in some clinical trials with one or two annual applications of 8% SnF2 than from three or four applications of sodium fluoride. However, this conclusion was not seen with other trials [11].

3.7 Acidulated Phosphate Fluoride

APF solutions and gels have shown most impressive evidence in support of its use, as a cariostatic reagent, over other agents [11]. After the application of APF, dehydration and shrinkage in the volume of hydroxyapatite crystals is seen forming an intermediate product called dicalcium phosphate dihydrate (DCPD) on hydrolysis. This shrinkage results in more fluoride penetration into the crystals more deeply through the openings leading to formation of fluorapatite [10]. Fernandez et al., 2017 has shown “in situ, that the enamel demineralization was inhibited by the combination of single application of a gel containing APF (12,300 ppm F) plus the daily use of a dentifrice (1,100 ppm F) which is as effective as a highly fluoridated dentifrice containing NaF (5,000 ppm F) [12].

3.8 Silver Diamine Fluoride

Silver diamine fluoride (SDF) is used for caries prevention or control of dental caries as it is an anti-caries agent. SDF is applied until the child is old enough to cooperate during dental treatment [13]. The concentration of the most commonly used SDF was 38%, which contains 44,800 ppm fluoride [14]. High concentrations of 38% SDF (44,800 ppm F; 253,870 ppm Ag) and 30% SDF (35,400 ppm F; 200,400 ppm Ag) was used by Chibinski et al. and concluded that high concentration of 38% provided greater efficacy in the prevention of dental caries in deciduous teeth than low concentrations [13]. To mask the staining of the cavitated lesions treated with SDF, self-curing glass ionomer cement is used. This technique has been referred to as silver modified atraumatic restorative treatment (SMART) [15].

3.9 Fluoride Containing Sealants and Restorations

Acoording to Kus¸go¨z et al. 2010, the incorporation of fluoride in resin-based FS inhibit demineralization of the adjacent tooth structure by releasing fluoride and recharge abilities which is lowered compared to glass ionomer sealants. It has been seen that fissure sealants forms physical barrier which inhibits the formation of occlusal dental caries as well as the progression of existing carious lesions (Azarpazhooh and Main,2008) [16].

3.10 Non-fluoridated Remineralising Agents

3.10.1 Tricalcium phosphate

Tricalcium phosphate (TCP) enhances the levels of calcium in plaque and saliva [17]. Remineralization properties are seen in Tri-calcium phosphates with the advantage of the calcium phosphate system, that does not effect the activity of fluoride in dentifrices and is stable in aqueous environment [18]. This material is available in two forms of α and β (β particles are less soluble than α particles) with calcium: phosphate ratio of 1:5 [19]. 5000 ppm sodium fluoride dentifrice and a 5% sodium fluoride varnish are the products available with TCP [4]. Rao R et al (2017) evaluated the remineralization potential of fluoride using control group with no surface treatment, ClinPro Tooth Crème, ReminPro paste, Duraphat fluoride varnish. The best remineralization potential was seen by ClinPro tooth Creme followed by Duraphat and ReminPro [8].

3.10.2 Amorphous calcium phosphate

The Amorphous Calcium Phosphate (ACP) technology has been developed and commercialized which is an unstabilized calcium and phosphate system where a phosphate salt (e.g., potassium phosphate) and a calcium salt (e.g., calcium sulphate) are delivered. They can be delivered separately (e.g., from a dual-chamber device) intra-orally or delivered in a product with a low water activity (Tung and Eichmiller, 2004) [20]. In 1999, ACP was first introduced as Enamelon by incorporating into toothpaste and later Church and Dwight reintroduced as Enamel Care toothpaste in 2004 [17]. “ACP and FACP are considered promising biomimetic materials to hinder demineralization of dental hard tissues in preventive dentistry” according to Iafisco M. et al (2018). The acid-etched dentin showed good ability to partially occlude the tubules and the demineralized enamel was restored into its native structure [21].

3.10.3 Casein phosphopeptides – amorphous calcium phosphate

Casein stabilizes the calcium and phosphate ions by releasing small sequences of peptides (CPPs) through partial enzymic digestion. This leads to the development of a remineralization technology based on casein phosphopeptide-stabilized amorphous calcium fluoride phosphate complexes (CPP -ACFP) and casein phosphopeptide stabilized amorphous calcium phosphate complexes (CPP-ACP) [4]. In 1998, Prof. Reynolds introduced a remineralizing agent at the school of Dental Sciences at the University of Melboune in Australia named as CPP-ACP (Tooth Mousse, GC India). There is a synergism in remineralising potential when CPP-ACP is combined with fluoride. CPPs enhances efficacy of fluoride as a remineralizing agent by keeping fluoride ions in solution by forming fluoroapetite [8]. Bailey et al., 2009 concluded that CPP-ACP cream treatment regressed more post-orthodontic white-spot lesions over a 12-week period [20].

3.10.4 Bioactive glass

Bioglass (BG) consist of calcium, sodium, phosphate, and silicate and belongs to class of bioactive material [6]. Bioactive materials have potential applications in tooth remineralisation and induce calcium phosphate formation. Hench & Anderson bioactive glass in 1969. Bioactive glass formulation consists of 6 wt% P2O5, 45 wt% SiO2 and 4.5 wt% Na2O and CaO [8]. A fluoride-containing bioactive glass (BioMinF; http://www.biomin.co.uk) was introduced recently in toothpastes as a caries remineralising and preventive additive [15]. Dr. Len and Dr. Hack introduced Novamin which is manufactured by Novamin technology and is a trade name for bioactive glass [8]. TahaAA et al (2017) extensively studied the Bioglass45S5 regarding the remineralization of white spot lesions. Remineralization potential was compared between CPP-ACP treatment, topical fluoride, bioactive glasses, and concluded that enamel remineralization is enhanced by bioactive glasses and is more effective [8].

3.10.5 Xylitol

Xylitol has been shown to have cariostatic effects as well as noncariogenic. It is a tooth friendly non-fermentable sugar alcohol [6]. The xylitol chewing gum enhances the protective properties of saliva by increasing salivary flow rate. This increases the concentration of phosphate and bicarbonate in stimulated saliva. As a result, phosphate and bicarbonate increases in plaque pH which in turn prevents demineralization of tooth structure by increasing the salivary buffering capacity. Moreover, calcium, hydroxyl and phosphate ions in higher concentration in such saliva also enhances remineralization [5]. Milburn et al. (2015) have shown the greatest

initial fluoride release in the first four hours in fluoride varnish, containing xylitol-coated calcium and phosphate, exceeding 10 times than that of other varnishes such as, Vanish, Duraphat® and Enamel Pro® [6].

3.10.6 Dicalcium phosphate dehydrate

DCPD readily turns into fluorapatite in the presence of fluoride as it is a precursor for apatite [6]. Walsh LJ, 2009 concluded that inclusion of dicalcium phosphate dehydrate (DCPD) in a dentifrice increases the levels of free calcium ions in plaque fluid when compared to conventional silica dentifrices, which remain elevated for up to 12 hours after brushing [17].

3.10.7 Nanoparticles for remineralisation

Recently, nanotechnology has attracted a great deal of attention [22]. Increased cumulative fluoride release on addition of nanoCaF2 was seen when compared to the traditional glass ionomer cements (Xu HHK et al.). When compared with traditional glass ionomer cements, the CaF2 nanoparticle (nano-CaF2) has a 20-fold higher surface area [6]. β-TCP nanoparticles with improved cariostatic and remineralizing properties can be prepared on the enamel surface [19]. Nano-HA increases the degree of remineralization in acidic conditions by aiding more ions diffusion in the center of the demineralized zone [23]. Addition of ACP nanoparticles in composite resins, adhesives and ionomer cements tends to be the source of calcium and phosphate ions [6]. Acoording to Sheng et al. (2016), nanoBG particles promote mineral formation on dentin surfaces and make dentin more acid resistant [24].

3.10.8 Polydopamine

Dopamine, regardless of type, size, and shape of hybridized counterpart materials, has been extensively used for biomaterial surface modification. Zhou YZ (2012) have found that demineralized dentin remineralization was promoted by polydopamine. It was seen that densely packed hydroxyapatite crystals occludes all dentin tubules [25].

3.10.9 Pa

Polyphenols have anti-inflammatory and antioxidant. Polyphenols are plant-derived substances. Proanthocyanidin (PA) is a polyphenol which is a benzene-pyran-phenolic acid molecular nucleus containing bioflavanoid. Proanthocyanidin, is free radical scavenger and a natural antioxidant. Collagen forms a proline–PA complex as it has high affinity for PA-based components (GSE is a powerful source of PA) and is a proline-rich proteins. There are four different mechanism by which the collagen cross-links increases in GSE: hydrophobic interactions, hydrogen bonding, ionic and covalent. It is expected that GSE is involved in the remineralisation of enamel defects by exogenous collagen crosslinks. Nagi SM et al (2019) evaluated that the positive effects of GSE hydrogels on the remineralization process of bleached enamel [26].

3.10.10 Theobromine

Two types of substances are present in theobromine which provides cariostatic property: One which exhibits anti-bacterial activity and the other anti-glucosyltransferase [27]. According to Amaechi et al., theobromine and fluoride toothpaste has given a significantly higher mineral gain with relative to artificial saliva showing the remineralising potential of theobromine [6].

3.10.11 Arginine

Arginine bicarbonate is an amino acid with particles of calcium carbonate, which adheres to the mineral surface. After the calcium carbonate dissolves, the release of carbonate may cause a slight rise in local pH whereas the released calcium is available to remineralize the mineral [6]. Recently, arginine incorporated into dentifrice formulations suppresses mineral loss via a buffering effect [Cummins, 2013a]. A superior effect of arginine-containing FD (AFD) has been observed in terms of the reversal of white spot lesions in many clinical studies over regular FD [Srisilapanan et al., 2013; Yin et al., 2013; Li et al., 2015a]. However, it is still under debate regarding its clinical significance [Ástvaldsdóttir and Östlund, 2017] [28].

3.10.12 Self-assembling peptides

A biomimetic technology was introduced about a decade ago to promote faster remineralization as minerals from saliva or supplied by other therapies need nucleation sites for precipitation and remineralization, (Kirkham et al. 2007) [29]. Under defined environmental conditions, rationally designed β-sheet-forming peptides P114 form three-dimensional scaffolds by self-assembling themselves. They nucleate hydroxyl

apatite de novo. Self-assembling peptides mimicks the action of enamel matrix proteins during tooth development and have been used in mineralized tissue regeneration [4]. Nowadays, P11-4 is available as a commercial products named as Curolox Technology (credentis ag, Windisch, Switzerland) [30]. Alkilzy et al. (2017) suggested that on promoting remineralization of early carious lesions, P11-4 in combination with F varnish (22,600-ppm F) is superior than F varnish alone. Others RCTs are currently registered (NCT02101255, NCT02020681, NCT02119507, NCT02913885, NCT02341872) [29].

3.10.13 Electric field-induced remineralization

Wu et al. have introduced this technique to shorten the mineralization time with the help of electrophoresis achieved in the absence of both calcium phosphates and their analogs. It also remineralize the completely demineralized dentin collagen matrix and [31].

4. CONCLUSION

The preventive approach of identification, conservation, and non-restorative treatment of incipient caries saves both dental manpower and expense and suffering for the patient. With a clearer understanding of the implementation of these remineralizing agents and new technologies accessible to dentists, one can create a more favorable relationship in which remineralization occurs more often than demineralization. And further requires more detailed clinical knowledge and trials along with a “watching brief” methodology necessary for this rapidly progressing area of dental science.

CONSENT

It is not applicable.

ETHICAL APPROVALS

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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