Unveiling promising materials and concepts in enamel remineralization - A comprehensive review

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***Abstract*- Rather than being a continuous, unidirectional process of the mineral phase's demineralization, dental caries is a cyclic occurrence that involves stages of demineralization and remineralization. The hydroxyapatite (HAP) crystal lattice can once again include minerals in their ionic forms leading to a natural healing mechanism called remineralization. This process takes place under almost neutral physiological pH circumstances. Research has been done on a wide range of remineralizing substances and procedures, many of which are now being utilized therapeutically with remarkably consistent favourable outcomes. This article's goal is to provide a quick update on the state of remineralization agents that are being used to "treat early caries lesion" noninvasively.**

***Keywords:* Remineralisation, recent advancement, nanoparticles, self assembling peptides.**

1.Introduction

Dental caries is a common disease characterized by demineralization and cavitation that damages teeth[1]. Preserving tooth structure prevents the progression of demineralization and potential decay. Over time, the sugars in the forms of glucose, fructose, and sucrose are converted into acids, which further lowers pH below 5.5 and causes demineralization. Similar to how saliva removes acid after sugar has lessened its impact and turns it into salts, raising pH over 5.5. Fluoride also causes the biofilm to become saturated, which triggers remineralization(Figure 1). Remineralization acts as a natural defence against the formation of dental caries. Enamel remineralization helps to restore and strengthen the mineral content of tooth enamel. Strengthening enamel inhibits the growth and progression of carious lesions. Reduction in porous enamel helps diminish sensitivity to hot, cold, or sweet stimuli. Effective remineralization may reduce the need for invasive dental restorations. In recent years, a number of remineralization-inducing drugs have been developed; most of them contain varying amounts of calcium ions, phosphate, and fluoride. When applied to the tooth's surface, these remineralizing agents are meant to regulate the cycles of demineralization and remineralization, which are determined by the microenvironment around the tooth [2]. The initial stage of tooth decay or demineralization is represented by the incipient carious lesions, which have the potential to develop to cavitation, be halted, or reversed. Sometimes called smooth surface caries or white spot lesions, they are active lesions that are limited to the enamel[3].The concept of minimally intervention dentistry (MID) incorporates remineralization, prevention, and minimal intervention in the placement and repair of restorations. The goal is tissue preservation, which entails treating the patient with the least amount of tissue loss feasible (ideally by avoiding illness and stopping its progression). It conveys an extremely accurate removal of the necessary tissue without endangering nearby tissue[4].
The article focuses on the enamel remineralization process and their recent advancements(figure 2)

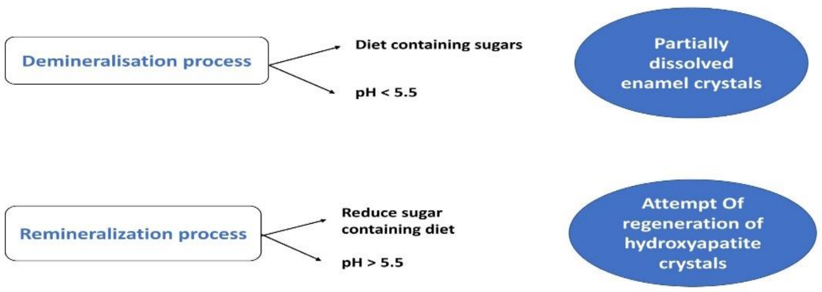


FIGURE — 1

- Nanotechnology Advancements:
- Biomimetic Strategies:
- Smart Materials and Drug Delivery Systems:
- Self assembling peptides(SAPs)
- Amorphous Calcium Phosphate (ACP)
- Tri – calcium phosphate (TCP)

- Collaboration of Remineralization Agents

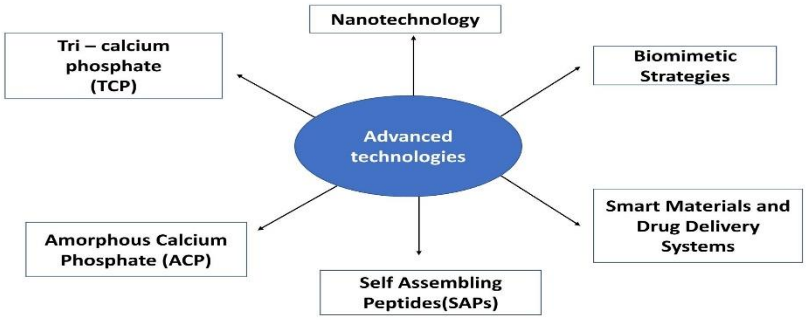


FIGURE — 2

II. Nanotechnology in Remineralization

In order to prevent bacterial development through a variety of processes, many nanoparticles, such as zinc oxide, silver, and polyethylenimine, have been added to dental adhesives and composites. These nanoparticles were effective in reducing the Lactobacillus acidophilus and S. mutans biofilms in an in vitro setting. It has been demonstrated that the application of antibacterial nanocoating to dental surfaces effectively eliminates bacteria, inhibits bacterial adhesion, and maintains the integrity of the bacterium when biological fluids are present[5]. Dental caries is treated using nanotechnology in two major ways (Figure 3) . In the first method, a process known as remineralization uses nanomaterials with the ability to release calcium and fluoride, such as calcium phosphate, calcium fluoride, hydroxyapatite, and fluorohydroxyapatite. The second strategy involves using antibacterial nanomaterials including zinc oxide nanoparticles, silver, and quaternary ammonium polyethyleneimine [6]. The commercially available products containing nanoparticles are 3M EPSE, Tetric Evo Ceram, Filtek supreme etc. Another newly proposed innovative formulation is nano-silver-fluoride-chitosan. It has been discovered that chitosan itself inhibits the growth of S.mutans, which is becoming more significant in the prevention of dental decay.

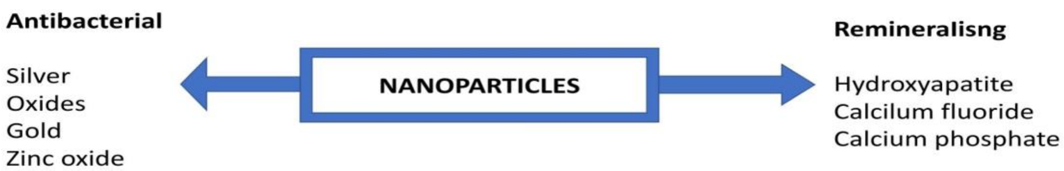


FIGURE — 3

III. Biomimetic Approaches in enamel remineralization

For remineralization ,bottom-up technique called biomimetic remineralization is utilized to make nanocrystals tiny enough to squeak into the spaces between neighbouring collagen molecules. Dentin matrix protein (DMP1) and dentin phosphophoryn (DPP, DMP2), which control the formation of HA crystal nucleation, are biomimetic analogues of non-collagenous proteins that stabilize these Nano precursor particles, also known as amorphous calcium phosphate (ACP) Nano-precursors. To encourage remineralization in this approach, a variety of bioactive substances and analogs of non-collagenous proteins (NCPs) have been employed[7]. Dr. Larry Hench created Bioglass®, or bioactive glass, in the 1960s. By mimicking the body's natural mineralizing characteristics and interfering with cell impulses, it functions as a biomimetic mineralizer that aids in the repair of tissue structure and function[8]. When they come into contact with bodily fluids, they become reactive and coat the particles' surface with calcium phosphate[1]. The resin modified Bioglass guides in preventing caries and inhibits early various lesion. (Figure 4)

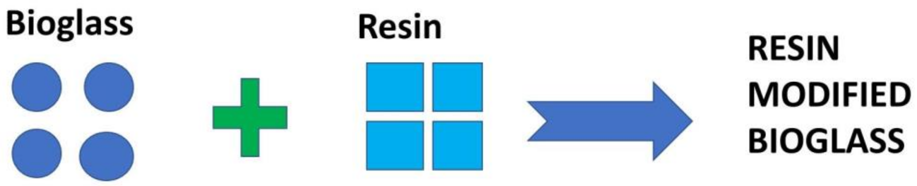


FIGURE — 4

IV. Smart Materials and Drug Delivery Systems

Smart materials, by definition and common consensus, are materials whose characteristics can be influenced by stimuli like pH, temperature, moisture, stress, and electric or magnetic fields. One of the main characteristics of intelligent behaviour is the capacity to revert to the initial condition following the removal of the stimulus[9]. Ideally, medications should be delivered to the target areas in a regulated way to maximize therapeutic effectiveness while minimizing adverse effects. The loaded medications possess "smart" properties, which they inherit from the controlled release nanoplatforms. Research on the phase transition of polymeric gels has increased significantly since Tanaka's observation of the phase transition of polyacrylamide gels in 1978[10] .Biomaterials that respond to stimuli have been developed gradually and are now routinely employed for regulated medication delivery. Pharmaceuticals may now be conjugated with various nanoparticles thanks to advancements in nanotechnology and nanomaterials. These substances react intelligently to variations in the pH of the oral cavity that are brought on by cariogenic bacteria. By releasing therapeutic ions when needed, they can buffer pH shifts, encourage local remineralization, suppress or kill bacteria, control the oral microbial community to prevent caries, and only activate antibacterial activity when the pH is low. Dental composites now contain a number of novel smart materials as active components, modified glass fillers, and changed resin monomers. Furthermore, the acid neutralization and remineralization of dental resins containing NACP were markedly improved by the combination of poly(amido amine) and NACP[11].

V. Self assembling peptides

The importance of peptide treatment has been highlighted by recent scientific developments, which have shown that it may both enhance mineral intake and reduce mineral loss from the tooth. HAP has been shown to be nucleated by the β-sheet-forming peptides P114, which, in certain environmental conditions, self-assemble to form three-dimensional scaffolds. HAP precipitates in situ when Ca++ ions are drawn to the anionic groups of the P114 side chains[1]. P114 is non-invasive, safe, and well-liked by patients. Utilizing a biomimetic peptide, like P114, has the added benefit of causing "natural" restoration by revitalizing the mineral. P114 is a well-tolerated procedure that is presently being tested to see if "next generation" peptides will speed up the healing process and enable "filling without drilling"[8]. It is important to use 2% sodium hypochlorite to eliminate the surface pellicle, and then apply 35% phosphoric acid for 20 seconds. The teeth must be cleaned and allowed to dry before the surface is examined for the existence of open holes. This is meant to provide room for the substance to enter the lesion and start the healing process. This process can also be aided by fluorides and other substances that promote remineralization. Because the process of remineralization is time-dependent, the peptide must be administered many times over the period of three to six months in order to have the desired effect[12].(Figure 5)

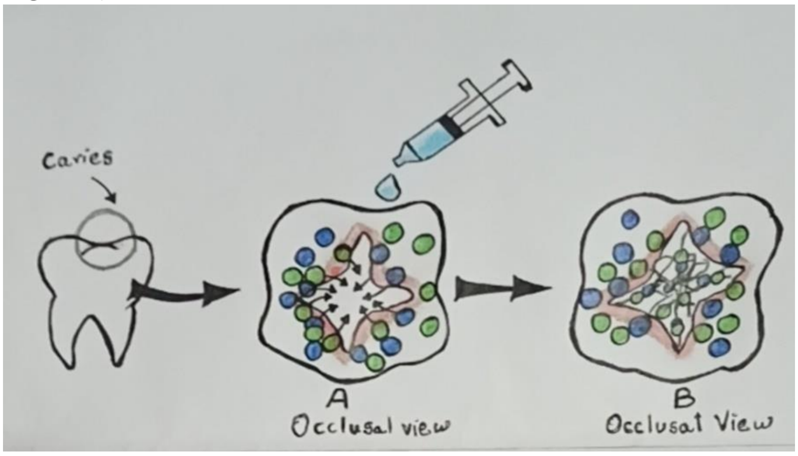


FIGURE — 5 Mode of action of self assembling peptides

a) Calcium hydroxide crystals around the caries gets attracted inwards and react with the peptides molecules,

b) The formation of new hydroxyapatite crystals in the scaffold

VI. Amorphous Calcium Phosphate (ACP)

Apatitic products, or ACPs, are the first solid phase to develop from a highly supersaturated calcium phosphate solution. It can change into solid crystalline phases, such as apatitic products or octacalcium phosphate, very fast. It serves as both a transient stage of biomineralization and a building block for bioapatite. The following steps have been proposed to explain how ACP converts to apatite at physiological pH: apatite ACP dissolves first, followed by the nucleation and development of a transitory OCP solid phase, which is then hydrolyzed by a topotactic process to yield thermodynamically more stable apatite[1]. Because CPP-ACP particles are easily soluble in saliva, they concentrate in plaque and serve as a calcium and phosphate ion reservoir. They release these ions in response to an acidic environment in order to prevent demineralization and encourage remineralization[13].The tryptic digestion of casein yields casein phosphopeptides (CPPs), which are then combined with calcium phosphate and refined by ultrafiltration. A helpful cario-static agent for the management of dental caries is CPP-ACP. Remineralization is produced by a dentifrice that combines CPP-ACP and fluoride; this is an improvement over both CPP-ACP and traditional dentifrices with high fluoride content. (Figure —6) [14]. The CPP – ACP was discovered by Eric Reynolds and also known as “Recaldent”. The CPP -ACP along with forms CPP -ACFP.

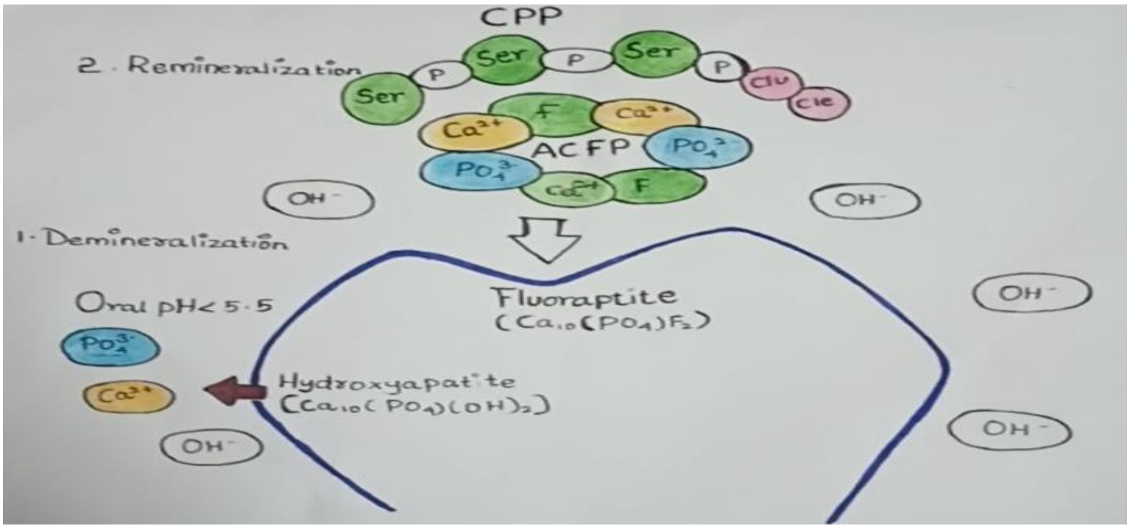


FIGURE — 6

Remineralization mechanism of CCP – ACP with flouride

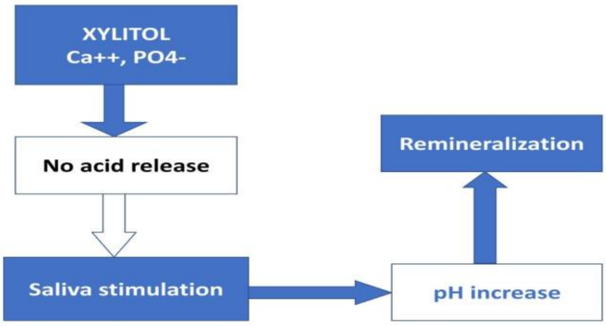
VII. Tri - calcium phosphate (TCP)

TCP is a novel hybrid substance that is produced by combining sodium lauryl sulfate, also known as fumaric acid, with beta tricalcium phosphate (ß-TCP). The purpose of this blending process is to produce “functionalized” calcium and “free” phosphate, which will boost the effectiveness of fluoride remineralization[9]. Using a mechanochemical ball milling technique, beta-TriCalcium Phosphate (β-TCP) and sodium Lauryl Sulfate (SLS) reacted to generate a functionalized calcium phosphate, which was then used to prepare a novel potential calcium system. An organic calcium phosphate hybrid is created as a result of the functionalization of tri-calcium phosphate during this procedure. This potential calcium system helps increase the remineralization advantages of fluoride by interacting with demineralized enamel. It gives the teeth more calcium and fluoride that is bioavailable[15].The protective layer dissolves when TCP eventually makes touch with the tooth surface and is moistened by saliva, allowing the teeth to access calcium, phosphate, and fluoride ions. In contrast to fluoride alone, the combination of calcium and fluoride then interacts with the weakening enamel to provide a seed for increased mineral development.

VIII. Collaboration of Remineralization Agents

According to the study of Ravi K Konagala et al, the remineralization capacity of nanohydroxyapatite and fluoride varnishes was greatly enhanced by the addition of arginine. Given that fluorides are toxic in high concentrations, this arginine-based combination may be able to provide sufficient remineralization at lower fluoride levels[16]. Danielle Mendes da Camara et al. came to the conclusion that adding 1% HMP to dentifrice containing 1100 ppm F leads in a larger inhibitory influence on enamel demineralization when compared to a regular dentifrice. This formulation might be a safe replacement to increase the advantages of conventional dentifrice (1100 ppm F) in preventing caries. In individuals who are at a high risk of acquiring caries, in particular, it might be beneficial in reducing the chances of caries in the population[17]. It has been demonstrated that xylitol, a nonfermantable sugar alcohol that is favourable to teeth, has both cariostatic and noncariogenic properties. By inactivating S. mutans and preventing plaque from producing acids and polysaccharides, it has antcariogenic property . An increase in salivary flow boosts the body’s ability to buffer acids, and a high mineral content provides the minerals needed to replenish the enamel’s damaged regions (figure 7) . According to research by Milburn et al., fluoride varnish with calcium and phosphate covered with xylitol had the highest initial fluoride release in the first four hours, more than ten times more than that of other varnishes like Vanish, Enamel Pro®, and Duraphat®[1] .

FIGURE — 7



It has antcariogenic properties by inactivating S. mutans and prevents plaque from generating acids and polysaccharides. Increased salivary flow helps the body buffer acids, and a high mineral content supplies the minerals that the enamel's damaged areas require to be replenished.

IX. Conclusion

Restorative dentistry has shifted its focus in recent years toward a conservative methodology, wherein remineralization operations are the best and recommended method for replacing damaged tooth structure. By identifying, preserving, and treating incipient caries non-restoratively, the preventative method saves dental staff, costs, and patient misery. It is anticipated that more research in this area will undoubtedly result in improved clinically applicable goods and technology with the best possible reactions and outcomes.

X. Conflict of Interest

Author declares no conflict of interests.

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