Biomimetic Agents: Novel Approach to White Spot Lesions - Review

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Abstract: ***Biomimetic remineralizing agents are compounds that replicate natural mineralization processes by emulating the bio mineralization mechanism. These active agents trigger remineralization by constructing three-dimensional structures resembling the extracellular matrix of teeth. Due to inadequate oral hygiene maintenance, white spot lesions (WSL) develop as subsurface porosities in enamel due to the demineralization process caused by caries. Clinically, they manifest as milky-white opacities on smooth surfaces. If not addressed, White Spot Lesions (WSLs) can advance to cavities and may also give rise to aesthetic concerns. Treating advanced caries requires more cost-effective prevention methods than surgical interventions. Contemporary dentistry aims to non-invasively manage white lesions through remineralization, with the goal of halting disease progression and enhancing the strength, appearance, and functionality of teeth. Various strategies exist to manage and prevent the advancement of white spot lesions, including the use of fluoride and desensitizing agents. Fluorides stands as one of the most effective and widely supported preventive measures, serving as a clinically proven remineralizing agent with ample scientific literature. In regions like India, where fluorosis is prevalent and potential side effects are a concern, biomimetic materials emerge as a promising avenue for biomineralization. These materials offer an alternative to fluoride agents and can also enhance the remineralization potential of fluoride. This review provides a succinct overview of the clinical applications and mechanisms of action of biomimetic agents for enamel remineralization.***

Keywords: Biomimetic, Biomineralization, Fluorosis, Fluorides, Remineralization, White Spot Lesion

1. Introduction

Almost 3.5 billion people worldwide are affected by oral diseases, and three out of four individuals impacted live in middle-income countries. According to WB country income level, oral diseases rank first of the most common non communicable diseases in the world. Among the major oral diseases, caries of permanent teeth is the most prevalent with around 2 billion cases [1]. White spot lesions (WSL), it is an early precursor of dental caries & more common in both orthodontic & non orthodontic individuals. Due to accumulation of dental plaque, the acidic by-products produced by cariogenic bacteria cause subsequent enamel demineralization and formation of WSLs [2]. In order to stop the demineralization process, aid to improve the remineralization and to stop the progression of enamel caries, some desensitizing agents & fluoride has been used for decades through its topical effect by forming fluorapatite crystals which is more resistant to acid attack than hydroxyapatite [3]. Fluorides excel at the process of enamel remineralization but do not have the capacity to encourage the development of well-structured apatite crystals. But biomimetic agents have the potential to regenerate the diseased enamel with hierarchical enamel microstructure. Most recently, biomimetic materials gained researchers attention as it is novel approach to treat white spot lesion. Biomimetic materials, including bioactive glass, self-assembling peptides, amelogenin, dentin phosphoprotein derivative 8DSS peptides and others, exhibit superior subsurface remineralization capabilities that have not been demonstrated by fluoride agents [4]. These materials have shown more promising outcomes in reducing white spot lesions compared to traditional fluoride varnishes, as evidenced by various studies [5,6]. As a result, they hold the potential to serve as alternatives to fluoride agents, with the option to enhance their remineralization effects by incorporating fluoride. The objective of this review is to provide insights into the clinical applications and mechanisms of action of biomimetic agents for enamel remineralization.

Bioactive Glass

Bioactive glass, which consists of amorphous sodium-calcium phosphosilicate. when this material comes into contact with saliva, sodium ions from the bioactive glass particles interact with hydrogen cations (in the form of H_3O^+) in the saliva, triggering the release of calcium and phosphate (PO_4^-) ions from the glass. During the initial exposure of the material to saliva, there is a temporary rise in pH due to the release of sodium ions. As a result of the pH increase, there is precipitation of additional calcium and phosphate ions, leading to the formation of a calcium phosphate layer. As these reactions progresses, this layer crystallizes into hydroxyapatites thus how remineralization occurs [7]. In a study conducted by Sayeeda Bangi et al in 2020 stated that BAG materials showed marked reduction of white spot lesion and it has the ability to remineralize the initial enamel caries lesion [8]. Bioactive glass dentifrices with fluoride had positive effects on the fluoride bioavailability & induces the formation of fluorapatite [9]. It has been used in various clinical application such as treatment of dentinal hypersensitivity and alveolar ridge regeneration because of alveolar defects. Researchers should further investigate the

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potential role of bioactive material impact on tooth remineralization to gain a deeper understanding of its influence.

Tricalcium silicate

Tricalcium silicate is a bioactive material it has also the ability to induce the apatite formation. It has both repair and protective properties whenever it contacts with saliva the silanol substance of TCS (Tricalcium silicate) dissolves and deposits on enamel surface further it binds to calcium ions induce the hydroxyapatite formation. Then salivary phosphate attracts the calcium ions helps in further remineralization and it also shows potential in remineralization of subsurface enamel lesions [10,11]. calcium silicate deposited on acid eroded enamel cause potential repair; calcium silicate deposited on sound enamel protects from acid challenge [12].

Nanohydroxyapatite

Nanohydroxyapatite is a bioactive substance with a chemical composition closely resembling that of apatite crystals found in human enamel. Because of the nano microcrystalline forms, it has the ability to adsorb the tooth surface and easily fill the enamel interprismatic space & bring about remineralization [13]. Hence, nanohydroxyapatite has been added in dentifrices, in the concentration of 10% results in Greater remineralizing effect compared to amine fluoride toothpaste on white spot lesions [14]. Huang et al conducted a study to determine the use of different concentrations (1%, 5%, 10% and 15%) of nanohydroxyapatite and their remineralizing capacities, concluded that 15% had a good remineralizing effect [15]. However, 10% showed almost similar results to 15% and could be used effectively. In fluoride dentifrices, the chance of systemic health risks is common such as fluorosis but the accidental ingestion of hydroxyapatite (HAP) as a toothpaste ingredient is generally not associated with systemic health risks. This is because hydroxyapatite is the primary inorganic component found in various human hard tissues, including teeth and bones. Consequently, nanohydroxyapatite can be considered as a potential alternative to fluoride for enamel remineralization agents.

CPP - ACP (Casein phosphopeptide - Amorphous calcium phosphate)

CPP-ACP stands out as the extensively researched non-fluoride remineralizing agent. Casein phosphopeptide-stabilized amorphous calcium phosphate (CPP-ACP) exhibits topical anticariogenic properties due to its capacity to stabilize calcium and phosphate in an amorphous state. In acidic environments, ACP separates from CPP, leading to an elevation in salivary calcium and phosphate levels. CPP then works to stabilize ACP in saliva, preventing calcium and phosphate precipitation and maintaining stable calcium levels. The localization of ACP within the dental biofilm by CPP-ACP helps buffer free calcium and phosphate ions, contributing to the preservation of ACP levels in saliva. This maintenance of an amorphous state of supersaturation concerning tooth enamel plays a role in inhibiting demineralization and enhancing remineralization. In conditions of low pH, typical of cariogenic attacks, CPP-ACP promotes the release of $Ca2+$ and $PO4$ 3- ions, thwarting the demineralization process and fostering remineralization through the precipitation of calcium and phosphate ions [16]. CPP-ACP is a biomimetic material that has demonstrated its efficacy and superiority to fluoride agents, thus emerging as a promising alternative [17].

Tricalcium Phosphate

Tricalcium phosphate exist in two forms as alpha and beta. At room temperature, β-TCP is the stable form, demonstrating moderate solubility in water. This bioavailable version of tricalcium phosphate, β-TCP, finds application in dentifrices. During acid challenges, it elevates calcium and phosphate concentrations in both plaque and saliva. However, incorporating both calcium phosphate and fluoride ions in oral care products poses issues, potentially resulting in the depletion of bioavailable fluoride ions due to interactions between the calcium phosphate phase and fluoride ions. To address this incompatibility of calcium phosphates and fluoride ions, functionalized TCP has been developed in which tricalcium phosphate particles have been ball milled with sodium lauryl sulphate which enhances the fluoride remineralization [18]. Research by Buckshey et al in 2019 demonstrated that a functionalized tricalcium phosphate toothpaste (f-TCPT) exhibits superior remineralization effects compared to a fluoride toothpaste with 1,000 ppm fluoride concentration [19]. Since there is a scarcity of studies in the existing literature, it becomes imperative to conduct thorough and comprehensive research to ascertain its viability as a remineralizing agent.

Self-assembling peptides

It is a monomeric peptide consists of 11 amino acids known as P11-4 & also a new bioactive material used for treating white spot lesions. In demineralized carious lesions, self-assembling peptide P11-4 forms a three-dimensional matrix within the subsurface body of an initial enamel lesion which mimics enamel matrix proteins further, attract the calcium ions and precipitate hydroxyapatite crystals, which will repair the lost enamel surface results in greater subsurface remineralization of white pot lesion [20]. In a non- controlled clinical trial conducted by A. Brunton et al states that a single application of a solution containing SAP (self-assembling peptide) led to an enhancement in the clinical appearance of class V white spot lesions [21]. The white spot lesion was regressed & significant increase in the subsurface microhardness also be observed in vitro after the application of SAP. The least intrusive technique for remineralization is SAP, and further studies conducted in vivo are necessary to validate its efficacy.

Amelogenin

Over the past few decades, there has been extensive research on remineralization in the presence of amelogenin, which has the ability to regulate crystal growth. Amelogenin is known to play a pivotal role in determining the form, organization, and growth of hydroxyapatites during the enamel mineralization process. However, in mature enamel, matrix proteins are absent, and tooth has completely mineralized so enamel microstructure is increased by using amelogenins [22]. A novel hydrogel, comprising amelogenin and chitosan, has been created for enamel reconstruction. It has been reported that this hydrogel can generate an enamel-like layer on an etched enamel surface, leading to a notable enhancement in the hardness of the previously etched enamel. They reported that these needle-like crystals, which are similar to the fundamental units of natural enamel within the prisms [23].

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The enamel layer formed by amelogenin takes a long time to develop, difficult to extract & store therefore, it is impractical for clinical application.

Dentine Phosphoprotein-Derived 8DSS Peptides

Dentin phosphoprotein (DPP) stands as the predominant non-collagenous constituent within the dentin extracellular matrix, and it is recognized for its significant involvement in the mineralization process of teeth. It has two mechanisms, firstly they limit the dissolution of $Ca2+$ and $PO43-$ ions from demineralized dentin and they actively promote the capture of these ions to form new mineral deposits on demineralized enamel [24]. Till date it has been proved in invitro studies not in in vivo studies. Drawback is that 8DSS binds calcium strongly it could lead to calculus formation if not in controlled circumstances [25]. hence future in vivo studies must be meticulously conducted to overcome these challenges.

Gamma-poly (glutamic acid)

Poly (D/L-γ-glutamic acid) represents a protein-like polymeric substance released extracellularly and produced through Bacillus subtilis fermentation. This material possesses impressive biocompatibility, osteoconductive properties, and bioactivity. γ-PGA solutions attach to the Hap (Hydroxyapatite) surface, persisting even after a 60-minute sustained exposure to acidic conditions, serving as a protective layer for the enamel surface i.e., shielding effect and promoting resistance to bioerosion. γ- PGA exhibits a saliva like viscosity and the ability to bind calcium ions. It bears a remarkable similarity to statherin, thus holding potential for employment as an anti-cariogenic agent and a therapeutic measure to counteract rampant caries [26]. Teng et al conducted a study to investigate a protective effect against the etching of teeth by the application of γ-PGA/nano-HAp paste he concluded that novel combination of γ-PGA/nano-HAP paste shows enhanced the tooth's microhardness and acid-resistant efficiency [27]. However, further studies are required to obtain clinical outcome of work.

Agarose hydrogel agarose

Agarose consists of a natural polysaccharide and has emerged as a novel category of biomaterials, due to its multifaceted biological capabilities, exceptional biocompatibility, and minimal toxicity. These attributes render agarose well-suited for various applications in fields such as tissue engineering and biomedicine. Its important action is in occlusion of dentinal tubules for dentinal hypersensitivity & it act as a scaffold produce enamel prism-like tissue helps in remineralization [28]. Further studies have to be conducted to determine its efficacy.

Poly (Amido Amine) Dendrimers

Poly (Amido Amine) Dendrimers are often referred to as "artificial proteins" because they have the ability to imitate the functions of natural structures in controlling the biomineralization process of tooth enamel. It Categorized into three types, namely amphiphilic, carboxyl-terminated, and phosphate-terminated PAMAM dendrimers exhibit a strong tendency to self-assemble into hierarchical enamel crystal structures. It has the potential to act as amelogenin analogues for biomineralization [29]. PAMAM dendrimers also attract the mineral crystal deposits, reducing the demineralization area and achieving mineralization beneath the surface (subsurface mineralization). PAMAM excels in adhering to enamel, functioning as a nucleation template, capturing calcium and phosphate ions to facilitate the generation of fresh mineral crystals, thereby accomplishing both the prevention and treatment of enamel caries. The newly generated crystals through the process of remineralization exhibit identical structure, alignment, and mineral composition as the original intact enamel [30]. Among 3 groups, PAMAM-OH showed the least remineralization ability, followed by PAMAM-COOH, with PAMAM-NH2 showed the best remineralization ability PAMAM dendrimers can be used a component of enamel-protective paint, mouthwash or therapeutic remineralization solution [31]. In addition, in vivo study has to be conducted to know the original behavior of PAMAM & effectiveness.

2. Conclusions

Among all the biomimetic materials CPP - ACP (Casein phosphopeptide - Amorphous calcium phosphate), nanohydroxyapatite, bioactive glass has showed better results in regression of white spot lesion based on clinical studies conducted so far, and other biomimetic materials are still under development hence in vivo multicentric trial has to be conducted by researchers to evaluate its efficacy. Another property is that subsurface mineralization which is not possible with fluoride remineralizing agents. Biomimetic agents along with fluoride gave excellent results in remineralization then fluoride or biomimetic agents alone. Biomimetic agents can also be implemented as a part of community programme like fluoride programmes, but still based on availability & cost, fluoride is gold standard and gives successful clinical results, some regions like where prevalence of fluorosis is more, biomimetic materials can be considered as better alternative to fluoride remineralizing agents. Future in vivo multicentric trials are required to prove its efficacy.

3. Recommendations

In developing nations such as India, approximately 25 million people are presently affected by fluorosis so, application of topical fluoridated agents is not applicable for managing white spot lesion (WSLs). Hence, Biomineralizing agents serves as a promising option for promoting remineralization. In India, only a limited selection of biomineralizing agents is currently available, including CPP- ACP (Casein phosphopeptide - Amorphous calcium phosphate), Bioactive glass (BAG), nanohydroxyapatite, and Tricalcium silicate. However, their cost is still higher compared to fluoride, making it challenging to implement these biomineralizing agents widely. To address this issue, public health programs should be initiated to raise awareness among the political systems & the population about these agents and encourage their use to reap the associated benefits. At the political level the taxes of these biomineralizing agents can be reduced hence making it available for the general public for use.

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