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Biomimetic Remineralising Systems – A Review

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ABSTRACT: Dental caries which is a common infectious disease, remains a challenge despite the widely implemented oral and dental health promotion programs. White spot lesions being the first clinical signs of imbalance between demineralization and remineralization can be dealt with using a biomimetic approach. Biomimetic approaches to stabilization of bioavailable calcium, phosphate, and fluoride ions and the localization of these ions to non-cavitated caries lesions for controlled remineralization shows great promise for the non-invasive management of dental caries. The main goal of minimally invasive dentistry is to manage non-cavitated caries lesions non-invasively through remineralization which prevents further disease progression and helps in improvingaesthetics, strength, and function. This review aims to highlight the development of biomimetic regenerative systems which may be the future, bringing us a step closer to the reality of growing artificial enamel.

KEYWORDS: White spot Lesions , RemineralisingAgent,Biomimetic Materials.

I. INTRODUCTION

[1]Dental caries is a common infectious disease of the dental hard tissue, which remains a challenge in dentistry despite the widely implemented oral and dental health promotion programs.[2]The development of Dental caries is a dynamic process, resulting in a mineral lossdue to an imbalance between demineralization and remineralization and tooth structure. [3]The early carious lesion observed clinically in the enamel is a white opaque spot. A substantial amount of information available from microradiography,polarised light experiments scanning electron microscopy, etc has enabled us to study the phenomenon and characteristics of white spot lesions. [3]According to available literature, the surface layer covering the white spot is porus but rich in minerals while the subsurface area is low in mineral content (10-70% vol). However, the surface morphology of the initial lesions is different from that of the sound enamel. The appearance of white spot lesions can be prevented by undertaking appropriate strategies in remineralizing these lesions. Research has shown good evidence on various noninvasive treatment modalities of white spot lesions, one of which is the use of fluoride and non-fluoride remineralizing agents. [4] "Extension for Prevention" has given way to the new paradigm of minimally invasive dentistry. The principles of micro dentistry are amazingly simple as compared to the principles of traditional operative dentistry. The adjuncts of traditional operative dentistry are centered on diagnosing and treating dental decay. In the late stages,the adjuncts of micro dentistry are centered on early diagnosis and intervention. One of the principles of minimally invasive dentistry is remineralizationn of the initial carious lesions which can be undertaken by the use of remineralizing agents.

[5]Fluoride is one of the widely recommended remineralizing agents for preventing white spot lesions worldwide. Despite its efficacy as a cariostatic agent it has certain limitations such as little /no infiltration into the lesion, does not eliminate the opaque appearance and careless handling of fluoride may lead to adverse effects such as fluorosis. [6]To overcome these a series of non fluoridated products such as cpp-acp,tricalcium phosphate, bioactive glass, and Acp technologies have been developed to promote enamel remineralization. Many systematic reviews and meta-analyses have analyzed the remineralizing potential of non-fluoridated agents and have reported these agents as substitutes for fluorides.[7]The currently available fluoridated or non fluoridated remineralizing agents are effective in remineralizing enamel but failed to promote the formation of organized apatite crystals. Hence there

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is an attempt to shift from reparative to regenerative biomineralization therapies.Biomimetic methods evolved from tissue engineering methods have demonstrated a strong potential for regenerating their biologicallysimilarenamel microstructure.[3]Therefore enhancing the remineralization may be a relatively less invasive and less expensive treatment option to arrest or reverse the disease process.

This review aims to highlight the development of biomimetic regenerative systems which may be the future, bringing us a step closer to the reality of growing artificial enamel.

DOES A REMINERALIZING AGENT REPAIR OR REGENERATE?

[5]Any external source /agent which supplies calcium and phosphate ions to the tooth to promote ion deposition into crystal voids in demineralized enamel to produce net mineralgain can be termed as a remineralizing agent.

[8,9]Ideal requirements of a remineralizing agent:

- Should deliver calcium and phosphate into the subsurface
- Should not deliver any excess of calcium
- Should not favor calculus formation
- Should work at an acidic pH so as to stop demineralization during a carious attack
- Should work in xerostomic patients also, as saliva cannot effectively stop the carious process
- Should be able to boost the remineralizing properties of saliva
- The novel materials should be able to show some benefits over fluoride
- To repair enamel in cases involving white spot lesions.

BIOMIMETIC MATERIAL: Biomimetic materials as remineralizing agents.

Biomimetics term coined by ottoschmitt is defined as the study of the structure and function of biological systems as models for the design and engineering of materials and machines.

[10]**BIOMIMESIS**: Is the process of synthesizing materials under suitable conditions mimicking the mechanism of development by natural means. A number of manmade materials and devices mimicking the natural ones to some extent have been introduced for implantation into humans with little or no success in the field of medicine and dentistry. However, no biomaterial developed to date has the same biological-physical, and optical properties as tooth structure. More research is needed in the field of biomimetic dentistry so that the dentist can work in union with nature and focus on recreating or regenerating biological tissues rather than repairing them. Recent advances in the field of remineralizationare the use of biomimetic materials which can be used to restore the mineral content and reverse the process of demineralisation.

[11]CLASSIFICATION OF BIOMIMETIC SYSTEMS IN REMINERALISATION :

Biomimetic systems :

TECHNOLOGY	COMMERCIAL PRODUCT
Dentin phosphoprotein 8DSS peptides	Not available
P11-4 peptides	Curodont Repair/Curodont Protect
Leucine-rich amelogenin peptides	Not available
Poly(amido amine) dendrimers	Not available
Electrically accelerated and enhanced remineralization	Not available
Nanohydroxyapatite	Apagard toothpaste/Desensin oral rinse

TABLE 1: BIOMIMETIC SYSTEMS

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DENTIN PHOSPHOPROTEIN 8DSS PEPTIDES :

[12]The extracellular matrix of human enamel is highly mineralized matrix consisting of 96% inorganic mineral and 4% organic material with water. The inorganic mineral is arranged in a highly complex three-dimensional micro and nanoarchitecture as crystalline hydroxyapatite (HA) that contributes to enamel's remarkable hardness.

[12]One of the noncollagenous extracellular matrix of dentin knownto play a critical role in tooth mineralization is Dentin phosphoprotein which is highly acidic (pH - 1.1),due to high concentrations of serine (45-50%) and aspartic acid (35-38%), which is unusually specific to calcium ions.[13] DPP-derived peptides may offer several potential advantages over entire proteins for dental remineralization as compared to intact DPPs. Peptides offer the advantage of being synthesized with high purity andoptimum shelf life. [14]Many studies have reported the generation of hydroxyapatite crystals using DPP in calcium phosphate solutions. Short functional peptides as compared to full-length DPP have been developed. [14]Short functional peptides have the advantage of high purity and better conformational fit on the enamel while avoiding allergies and immunogenicity associated with animal proteins.The octuplet repeats of aspartate-serine-serine, 8DSS peptides, are the most active derivatives of DPP in mediating biologically directed mineral deposition. [15]The 8DSS peptides offer an advantage of binding strongly not only to free calcium and phosphate ions but also to the hydroxyapatite surface. Thus application of these peptides to enamel not only prevents the dissolution of calcium and phosphate ions but promotes the uptake of these ions from the surrounding medium. Studies have shown a strong evidence that the newly grown minerals had improved properties such as reduced surface roughness, higher hardness and elastic modulus along with uniform deposition of apatite crystals.[15] However these studies have been conducted invitro and pose some challenges when used clinically such as enzymatic degradation in the oral cavity and increased calculus formation due to the strong binding of calcium ions. The challenges can be overcome by confirming the efficacy of 8DSS peptides by using then in invivo studies. These peptides hold a great promise as a substitute for fluorides.

AMELOGENIN PEPTIDES :

[16]One of the components of the organic matrix in enamel that plays a critical role in regulating the growth shape and arrangement of hydroxyapatite crystals during enamel mineralisation are amelogenins.The mineral loss caused by demineralization cannot be regenerated as mature enamel lacks these proteins. [16]Synthetic amelogenin-based systems such as recombinant porcine amelogenin (rP172) have been proposed to simulate the complex enamel microstructure. The calcium phosphate clusters and the enamel crystals produced by (rP172) were shown to be similar in hardness and elastic modulus to the native enamel.

[17]Leucin-rich amelogenin peptide comprisingof 56 aminoacids is an excellent low-cost and safer alternative to full-length amelogenins.[18] Reduced lesion depth and biomimetic reconstruction of enamel due to the linear growth of mature enamel crystalswere observed when enamel lesions were treated with Leucine-rich amelogenin peptide in in-vitro studies. However one of the disadvantages of amelogenin-mediated enamel regeneration is the difficulty to extract and store the protein. [18]More time is required for the growth of the repaired enamel layer, thus making it unsuitable for clinical use. [16]Although in-vitro studies seem to prove amelogenin mediated hydroxyapatite formation there is yet no evidence that a similar process of biomineralization occurs invivo, suggesting the need for studying amelogenin in invivo conditions.

POLY(AMIDO AMINE) DENDRIMERS :

[19]PAMAM dendrimersalso called nucleation templating analogs or artificial proteinsfor biomineralization, are highly branched polymers with internal cavities and a large number of reactive terminal groups. These amelogenin-inspired dendrimers can mimic the functions of the organic matrix thereby modulating the mineralization of tooth. The new crystals created by PAMAM have the same structure orientation and the mineral phase of intact enamel has been seen in studies conducted by Chen et.al .these dendrimers can help in overcoming the difficultiesof extracting purifying and storing the natural protein as they have the potential to act as amelogenin analogs.[20] Like the enamelins, the PAMAM mediated remineralization is also a time-consuming process, hence their clinical application may not be feasible in real-life scenarios.

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ELECTRICALLY ACCELERATED AND ENHANCED REMINERALIZATION :

EAER works by using iontophoresis to apply a small electrical field from a custom-made dental device to drive mineral molecules from a reservoir into the deepest parts of caries lesions, which have been cleaned and conditioned.

[21]EAER was developed to target the initial and moderate enamel lesions.The objectives of using this technology include 1) preservation of healthy enamel tissue. 2) restoration of the full depth of the carious lesions, thereby improving the mechanical properties. EAER does not regenerate the lost enamel via matrix proteins or the deposition of calcium and phosphate in these matrix proteins. [20]The advantage of EAER is that it utilizes the tools and chemicals commonly available in dental practice. Invivo studies are required for a thorough evaluation of its remineralizing potential, although the in-vitro studies show promising results in the remineralisation of carious lesions.[21]The essential steps in using EAER (electrically accelerated and enhanced remineralization) to restore caries lesions to the equivalent of healthy enamel: 1) precondition the lesion and its interior surfaces; 2) activate the interior surfaces of the lesion to receive remineralizing agents; 3) remineralize by driving minerals deep into the subsurface caries lesion via iontophoresis; and then 4) maturation whereby the repaired lesion achieves optimal hardness following treatment.

NANOHYDROXYAPATITE :

[22]Nano-sized HAP (n-HAP) is similar to the apatite crystal of tooth enamel in morphology and crystal structure. So it can be substituted for the natural mineral constituent of enamel for repair biomimetically.[23]The biomimetic effect of the nano-hydroxyapatite is based on its interaction with biological tissues and on its ability to mimic biogenic materials in their functionalities. Chemical composition is similar to enamel and dentin, with intermediate characteristics. The gradual action of biomimetic nano-hydroxyapatite crystals allows the linkage to dentinal and enamel tooth surfaces due to bio-reabsorption properties under physiological conditions. [22]This property can be modulated by ion substitution and crystallinity degree achieved by implementing innovative synthesis with nanosized crystal control.

CONCLUSION :

Fluoride is a gold standard material that has been available for decades for the remineralization of early carious lesions.Due to the inherent adverse effects associated with the use of fluorides, there was a new search in the development of non-fluoride remineralizing systems.It is the need of the hour to mimic and adopt the strategies available from nature to produce functional structures.Many biomimetic materials discussed in the present review have proven efficacious in in-vitro conditions.However long-term invivo studies are needed to understand the interaction of these synthetic biomimetic materials in the remineralization of carious lesions,making these newer agents commercially available for use is also a challenge with the growing research in these biomimetic technologies may bring us closer to the reality of growing artificial enamel.The era of preventive and minimally invasive dentistry clearly dictates the need for developing newer approaches to remineralize enamel caries lesions.

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