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Non-Fluoridated Remineralizing Agent-A Narrative Review

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ABSTRACT:

The goal of up to date dentistry is to manage non-cavitated carious lesions non-invasively through remineralization in an effort to stop disease progression, and to spice up, esthetics, and performance of teeth. The stress is presently being given to new technologies for enamel remineralization that means the changes within the understanding of dental caries. Further studies are required on biomimetic molecules involved in calcium fluoride phosphate stabilization and nucleation that may provide further improvement in the development of novel remineralization treatment. The aim of this paper is to review the up to date non-flouridate dremineralization system out there and its idea of action on tooth for remineralization. A search was of articles from ‘Pubmed” and “google scholar” with the keywords Remineralization-demineralization, casein derivatives, non-flouridated

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remineralizing agent was conducted. So, in this paper the current concept further bridges the standard gap between prevention, non-invasive and surgical procedures which is simply what dentistry needs for this age.

Keywords: Enamel caries, demineralization-remineralization, Non-fluoridated agent, Casein derivatives, Theobromine, Xylitol, self-assembling peptide.

Introduction:

Dental caries is a major public ill-health in most developing countries. It's one of the foremost common and preventable diseases of childhood.[1] In recent decades, though the frequency of dental caries has greatly decreased with the event of diagnostic strategies, prevention, and treatment of caries, the situation is still of concern for high-risk individuals team, especially youngster .[2]

Carious lesions usually develop more quickly in primary dentition than in permanent dentition because of distinct enamel structure and dietary habits of kids. The enamel structure in primary dentition is thinner, and therefore the surface micro-hardness is comparatively lower, compared with that of the permanent dentition. Also, primary dentition doesn't have a well-organized structured crystal arrangement, and comparatively is less mineralized. This variation leads to more susceptibility to caries and quicker caries progression in the primary dentition. Children show a greater consumption of sugar and acidic drinks that contributes to the higher caries prevalence in the primary dentition.[3]

Carious process involves a continuing shift within the demineralization-remineralization cycle. Remineralization is expedited by the buffering action of saliva, permitting calcium and phosphate ions to precipitate onto the tooth and form new mineral. Therefore, modulation of the demineralization-remineralization balance is that the key for prophylaxis of dental caries.[4]Remineralization of white spot lesions and carious lesions is presently attainable by a goodsort of agents like fluoride, bioactive calcium and phosphate, casein phosphopeptide-amorphous calcium phosphate, self-assembling peptide[5]. Although fluoride has a profound impact on the amount of caries progression, it is far from being a complete cure. On the opposite hand, presence of calcium and phosphate, and fluoride ions present in human saliva has a reparative impact on enamel erosion by depositing new mineral content to push remineralization.[6]

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The "minimal invasive" approach combines with earlier diagnosis and treatment of caries lesions as shortly as possible and accentuates prevention[7]Recently, investigators have primarily centered on calcium phosphate-based technologieswhich can further enhance fluoride' sability to revive the mineral loss. This can be achieved through various non-flouridate dremineralizing agents[8]. The current concept further bridges the aged-old gap between prevention, non-invasive and surgical procedures which is the ardent need for dentistryin this age.

Thus, the present review aims to provide in-depth information of various non-flouridate dremineralizing agent which will be use to treat white spot lesions.

Demineralizing- remineralizing cycle

Demineralization is the process of removal of mineral ions from dental enamel. It begins at the atomic level on the crystal surface within the enamel or dentin and can continues unless halted with the endpoint being cavitation[9]. It happens by disassociation of lactic acid, produced by microorganism sugar metabolism with tooth mineral loss. The reaction ends up in unleash of mineral ions into the solutions:

$Ca_{10}(PO_{4)6}(OH)_2 + 14H^+ \rightarrow -10Ca^+ + 6H_2PO_4 + H_2O$

The extent to that tooth mineral dissolves in an exceedingly given solution is ruled by the thermodynamic ion activity product (IAP):

$IAP= (Ca^{+2})^{10}(PO_4^{3-})^6(OH)^{-2}$

When IAP equals to solubility constant Ksp, the solution is in equilibrium with the solid and is alleged to be saturated. Demineralization occur once IAP within the demineralizing solution is less than solubility constant (Ksp).[10]

The subsurface lesion is reversible via a remineralization process. Remineralization is the process by which partially demineralized enamel is repaired through recrystallization of tooth enamel mineral salts. Carious remineralization occurs when there is supersaturation of saliva with respect to calcium and phosphate and increase in oral fluid uptake of calcium and phosphate drives the remineralization process.[11]

Over the course of human life, enamel and dentin undergoes unlimited cycles of demineralization and remineralization.[12] When the pH decreases below 5.5(critical pH), undersaturation happens with regard to hydroxyapatite (HA) then reaches the biofilm fluid,

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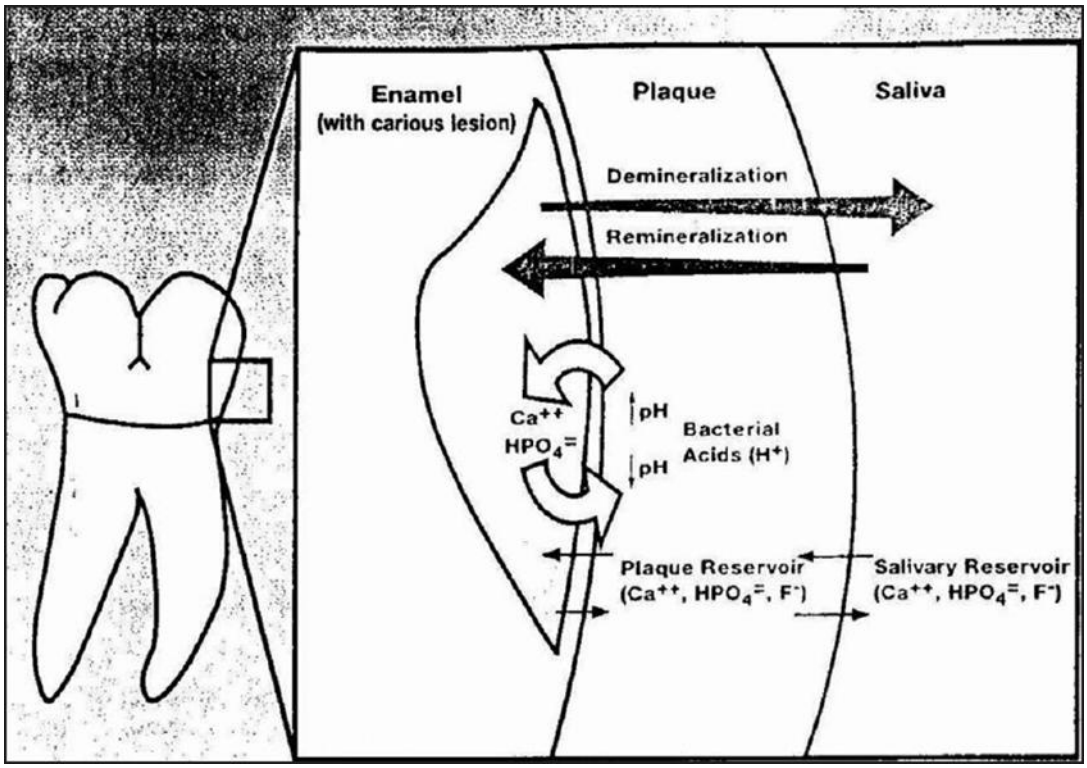
leading to mineral dissolution. Localized acids produced by plaque after a cariogenic challenge lowers the surface pH of the tooth and starts diffusing from the tooth, which leads to leaching of calcium and phosphate from the enamel. At this time, the plaque pH may have dropped to 4.0-4.5. This mineral loss leads to weakening of the mechanical properties and may leads to cavitation. When oral pH returns close to neutral, Ca2+ and (PO4)3− ions in saliva incorporate themselves into the depleted mineral layers of enamel as new apatite. The demineralized zones in the crystal lattice act as nucleation sites for new mineral deposition.[13]**(Fig 1)**

Fig 1: **pH is below critical pH 5.5, demineralization occur. Ca^{++} and PO^{4-2} leach in the surrounding saliva. When oral pH returns to near neutral, Ca^{2+} and PO^{4-2} ions in saliva incorporate themselves into the depleted mineral layers of enamel as new apatite**.



Why non-fluoride strategies?

1. Fluoride is extremely effective on smooth-surfacecaries, however, its impact is more restricted on pit and fissure caries.
2. A high-fluoride strategy cannot be followed to avoid the potential for adverse effects (e.g., fluorosis) because of overexposure to fluoride.
3. Toxicity of fluoride will be increased with inadequate nutrition.

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4. Though fluoride has had a profound impact on the level of caries prevalence, it is far from a complete cure.
5. Certain countries do not have fluoridated products.[14]

Ideal requirements of a remineralization material (Wash et al,2009)

1. It should diffuses into the subsurface or delivers calcium and phosphate into the subsurface.
2. Shouldn't deliver an excess of calcium.
3. Should not favour calculus formation.
4. Should work at an acidic pH.
5. Should work in xerostomic patients.
6. Ought to boost the remineralizing properties of saliva.
7. For novel materials, it ought to show a profit over fluoride.[15]

NON-FLOURIDATED REMINERALIZING AGENT:

1. **Casein phosphor-peptides-amorphous calcium phosphate (CPP-ACP):**

   Casein, a milk phosphor-protein predominent in bovine milk is present primarily as calcium phosphate stable micellular complexes and accounts for almost 80% of its total protein.[16] Cluster of peptides, referred to as casein phosphor-peptides (CPP), are shown to stabilize calcium and phosphate, conserving them in associate amorphous or soluble form termed as amorphous calcium phosphate (ACP).[17] It was discovered by Prof. Reynolds at the varsity of dental science at the university of Melbourne in Australia. CPP contains cluster sequence- Ser(P)-Ser(P)-Ser(P)-Glu-Glu- and incorporates a exceptional ability to stabilize calcium and phosphate as nanoclusters of ions in an exceedingly constancy solution.[18]

   Mechanism of action:

   Casein phosphor-peptides shows high bioavailability of calcium from milk and other farm products. CPP shows the flexibility to bind and stabilize calcium and phosphate in solution. Furthermore, it binds to the dental plaque and tooth enamel. Insoluble calciumphosphates aren't easily applied and does not localize effectively at the tooth surface.[17]Additionally, acid is required to produce ions capable of disseminative into enamel subsurface lesions.[18] However, the CPP keeps the calcium and phosphate in an amorphous, non-crystalline state. In this amorphous state,

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calcium and phosphate enter the tooth enamel and promote remineralization of enamel.[14,17]

Advantage:

- It localizes ACP in the dental plaque and buffers the free calcium and phosphate ion.[9]
- It enhances the effectualness of fluoride ions as remineralizing agent.[9]
- It gets incorporated into the pellicle in exchange of albumin and thus inhibit the adherence of Streptococusmutans and Streptococcus sobrinus and thus enhances remineralization.[19]
- CPP-ACP accessorial to soft drinks reduces their erosive potential on enamel.[20]

Disadvantage:

- It is pH responsive i.e with increase in pH the level of bound ACP increase, stabilizing free calcium and phosphate.[18]

Commercially named products:

RECALDENTTM (CPP-ACP) & GC Tooth Mousse/Prospec MI Paste

Related studies:

Sitthisettapong et al[21]conducted a clinical trial to test the impact of daily application of 10% w/v CPP-ACP paste for 1 year accessorial in regular dentifrice with fluoridated dentifrice in pre-school children for prevention of caries and concluded that the accessorial effect has no significant results in prevention of caries in the primary dentition.

Vashist et al[22] conducted a study to know the role of CPP-ACP in remineralizing of WSLs and inhibition of Streptococcus mutans comparing CPP-ACP with fluoride containing toothpaste and the results concluded that CPP-ACP containing toothpaste has slight remineralizing effect on the WSLs in 3-months evaluation. However, longer observation is usually recommended to confirm whether the greater change in WSLs is maintained.

To conclude, there's in depth clinical and laboratory studies conducted and CPP-ACP is safely and effectively administered. It is proven to bind prompltly to pellicle, plaque and soft tissue when applied in oral cavity.

2. **Amorphous calcium phosphate (ACP):**

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The ACP technology was developed by Dr. Ming S Tung in the year,1999, ACP was incorporated into dentifrice known as Enamelon and later introduced in 2004 and referred to as Enamel Care dentifrice by Church and Dwight. ACP technology needs a two-phase delivery system that keepthe calcium and phosphorous component from reacting with each other before use.[14]

Mechanism of action:

Two-phase delivery system is a unstabilized calcium phosphate system incorporated into a dual-chamber fluoride dentifrice with the intension of separately delivering calcium and phosphate ions into the mouth. On brushing, the intraoral mixing results in immediate precipitation of ACP on the tooth surface. This precipitate readily dissolves into saliva making it available for remineralization.[23,14]

Advantage:

- Useful adjunct for management of caries in orthodontic treatment.[14]

Disadvantage:

- Calcium and phosphate aren't stabilized, permitting the 2 ions to mix into insoluble precipitates before they are available to come in contact with saliva or enamel.
- Unstabilized calcium phosphate system promote dental calculus deposit on tooth.
- It rapidly sequesters free F- ions within the oral atmosphere, thus reducing the provision for lesion remineralization.[24]

Commercially named products:

ENAMELONTM and EnamelCare. It is also available as Discus Dental's Nite White Bleaching Gel and Premier Dental's Enamel Pro Polishing Paste. It's additionally employed in the Aegis product line as pit and fissure sealant, produced by Bosworth.[8]

Related studies

Papas et al 2008[25] showed evidence for ACP technology in single RCT in radiation patient where it was found to be superior to conventional fluoride dentifrices in lowering root caries, though its ability to regulate coronal caries is insignificant. Considering the limited evidence and better alternatives available, oral products based on ACP remineralization technology have restricted clinical applicabilitry.[24]

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3. Functionalized Tricalcium phosphate (f-TCP):

It is a hybrid material produced by milling technique that comprised of fused beta tricalcium phosphate (TCP) and sodium lauryl sulfate or fumaric acid. This mixing results in "functionalized" calcium and a "free" phosphate, designed to increase the effictualness of fluoride remineralization.[25] The purpose of funtionalizing β-TCP is to create a barrier preventing premature fluoride-calcium interaction, thereby permitting it to act as a targeted low- dose delivery system once applied to teeth.[26,10]

Mechanism of action:

β- TCP is similar to apatite structure and has a unique calcium environment where phosphate floats freely. When TCP comes in proximity with the tooth surface and is wet by saliva, the protective barrier breaks down making calcium, phosphate and fluoride available to the tooth. The fluoride and calcium then react with the feeble enamel to strengthen mineral growth. TCP provides catalytic amount of calcium to augment the efficacy of fluoride.[27]

Commercially available as:

5000 ppm fluoride dentifrice as Clinpro® 5000 introduced by 3M ESPE.

Related studies:

K.J. Chen et al [28] conducted a 24- months randomized controlled trail to compare the effectiveness of 2 fluoride application protocols in arresting dentine caries in primary teeth with 25% silver nitrate (AgNO3) solution followed by a commercially available varnish with 5% sodium fluoride (NaF) containing functionalized tricalcium phosphate (f-TCP). He concluded that when 25% AgNO3 solution, followed by a commercially available 5% NaF varnish with f-TCP when applied semi-annually, is more effective in arresting dentine caries in primary teeth than without f- TCP semi-annually.

4. Sodium calciumphosphosilicate (Bioactive glass):

Bioactive glass was invented by Dr. Larry Hench in 1960s. It acts as a biomimetic mineralizer that matches the body's own mineralizing traits and additionally affects cell signalling in an exceedingly manner that benefits the restoration of tissue structure and function.[29]

Mechanism of action:

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When in contact with saliva or water, it initially releases sodium ions. This elevates the pH scale into the range essential for Hydroxyapatite formation (7.5-8.5). Calcium and phosphate ions were released to compensate the normal levels found in saliva, this eventually increases ion concentration and precipitate in the tooth eventually and forms calcium hydrocarbonate apatite (HCA) to remineralize the defect.[14,9]

Advantage:

- It has the flexibility to impede dentinal tubules, therefore, helps in reducing tooth hypersensitivity.[30]
- It can be employed in patients with systemic problems such as ovulation, pregnancy, and during menopause where salivary secretion is insufficient.[10]

Commercially available as:

- Novamin®, a trade name for bioactive glass, manufactured by Novamin Technologies Inc. (Alachua, FL, USA).

Related studies:

Mohanty P conducted an in-vitro study to evaluate the remineralizing potential of Novamin by analyzing the Ca/P ratio of enamel samples around the orthodontic brackets. On comparison with a control group, Novamin was suggested as a potential novel remineralizing agent.[31]

5. **Nano-Hydroxyapatite:**

Hydroxyapatite (HA) is the main inorganic element of enamel and accounts upto 95% by weight of total weight of enamel. It contains 20-40nm particles HA. Hydroxyapatite is able to absorb glucan which is produced by S mutans with salivary protein which further enhances inhibition of plaque formation.[32]

Nano- Hydroxyapatite improves the repairing effect of enamel by reducing the dimension of enamel to a nano-scale, therefore a smaller HA is closer to a biological apatite when compared to a larger HA particle.[33]

A concentration of 10% nano-HA is optimal for remineralization of enamel.[34]

Mechanism of action:

Nano-hydroxyapatite repairs and prevents initial lesions in enamel because of its size and high availability of calcium and phosphate ions, that plays an important

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role in demineralization and remineralization process.[34] Low level of calcium in plaque are found to be indicative of caries incidence but not for phosphate ions.[35]The pH level affects the concentration of calcium and phosphate ion in-case of nano-hydroxyapatite. In the pH study, where highest degree of remineralization was seen in pH 4.0 than at pH 7.0, as the pH value decreases, the concentration of calcium and phosphate increases and more mineral deposit at the body of the lesions as the pH value of nano-HA decreased.[34]

In SEM analysis, nano-HA adheres to the pores created by demineralization and combines into small clusters then forms a uniform apatite layer on demineralized surface and covers the prismatic and interprismatic enamel surface.[36]

Advantage:

- Biocompatible and bioactive material.

Related studies:

Tschoppe P et al[37] has done an in-vitro study to judge the result of nano-hydroxyapatite dentifrice on remineralization of bovine enamel and dentin and observed that toothpaste containing n-HAP shows high remineralization effect compared to amine fluoride dentifrice.

6. Grape seed extract:

Root caries is especially prevalent among the elderly population due to gingival recession and exposure of susceptible root surface. Grape seed extract contains polyanthocyanidin which is an antioxidant and interacts with microorganism cell membrane protein and lipid and helps in lysis of cell wall thereby arresting root caries.[38]

Mechanism of action:

Polyphenols are plant -derived substances that have antioxidant and anti-inflammatory properties. One such polyphenol is proanthocyanidin (PA). PA is a naturally occurring plant substance present in fruits and vegetables. It strengthens the collagen-based tissue by increasing collagen cross-links and inhibits glucosyltransferases and acid production by S.mutans.[39]

Related studies:

Xie et al.[40] recommended the grape seed extract could contribute to not solely the deposition of mineral on the superficial layer of the lesion however additionally

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interact with the organic portion of root dentin through PA -collagen which interact stabilizing the exposed collagen matrix.

7. THEOBROMINE:

Theobromine (3,7dimethylxanthine) is a white crystalline powder of methylxanthine family. It differs from caffeine by just one methyl group (1,3,7dimethylxanthine) It is a water-soluble, crystalline, bitter powder found in chocolates along with tea and other foods.[41]

Mechanism of action:

It is believed that theobromine, in the presence of calcium and phosphate forms hydroxyapatite crystallites of an exaggerated size that strengthens the enamel thus making it less vulnerable to acid attack and exhibits anti-glucosyltransferase and inhibit activity of S mutans.41

Advantage:

- Easily absorbed and metabolized within the human body.[42]
- No adverse side effect such as dental fluorosis, tooth discoloration and gastric irritation with high dose.[43]

Related studies:

Testuo et al[44] conducted an in-vitro study on comparing Theobromine with fluoride dentifrice and found out that theobromine is a better alternative than fluoride and can be used as an ingredient of dentifrices and even if it is engulfed accidently, there's no adverse result.

8. Self-Assembling peptide:

Peptide treatment for incipient carious lesion is the latest area of research. Peptide treatment considerably increases net mineral gain attribute to the combined effect of increased mineral gain and inhibition of mineral loss.

Mechanism of action:

β-sheet forming peptide P114, itself assembles themselves to create three dimensional scaffolds beneath defined environmental conditions which nucleate the hydroxyapatite de novo and facilitate mineral tissue regeneration therefore it mimics the action of enamel matrix proteins throughout tooth development. At certain peptide concentration, P114 switches form a low viscosity isotropic liquid to a elastomeric

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nematic gel (pH <7.4). The anionic group of the P114 facet chains attracts calcium ions inducing precipitation of hydroxyapatite inducing mineral deposition.[45]**(Fig 2)**

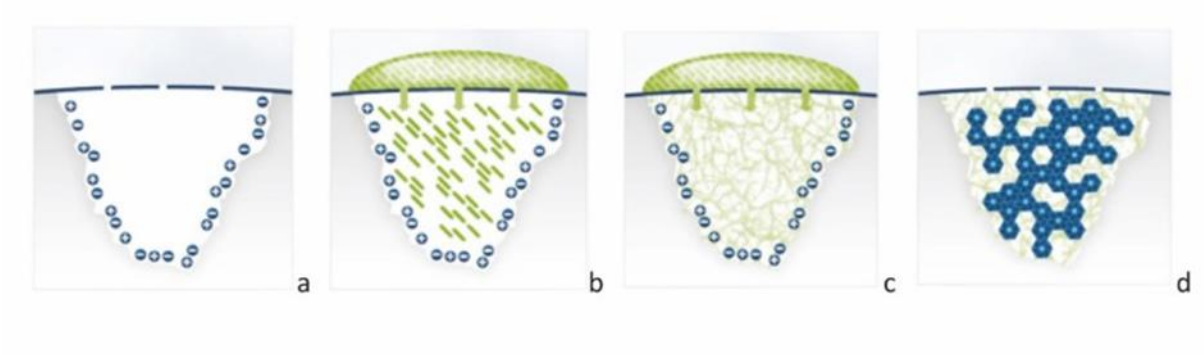

Fig 2. Ilustrate treatment of a carious lesion by the self-assembling peptide P11-4. (a) Initial carious lesion. (b) A drop of monomeric self-assembling peptide P11-4 is applied on the lesion surface; the monomers diffuse into the lesion. (c) P11-4 assembles within the carious lesion, forming a 3D scaffold. (d) De novo hydroxyapatite crystals form around the self-assembling peptide scaffold.

Advantage:

- Biomimetic material that induces repair by regenerating the mineral itself.

Commercially available as:

Curodent TM repair.

Related studies:

Schlee el al proved that when P114 is applied on tooth, the peptide diffuses into the subsurface micropores and forms 3D scaffold that is made up of small fibers and these scaffold mimics proteins found in teeth development and supports hydroxyl apatite crystallization around it over a period of 3 months.[46]

9. Calcium carbonate carrier- SensiStat:

The SensiStat technology is made of arginine, bicarbonate, an amino acid complex and particles of calcium carbonate which is a common abrasive found in toothpastes. This arginine complex is responsible for adhering calcium carbonate particles to the mineral surface.[14]

Mechanism of action:

The prime reaction is that the highly soluble arginine bicarbonate component is surrounded by poorly soluble calcium carbonate component, and because of its

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adhesive property it forms a paste like-plug that not solely blocks the dentinal tubules however additionally adheres to the tubule walls and slowly releases calcium that is then available to remineralize the tooth surface. Still, studies are underway to determine whether SensiStat can be used to treat early surface demineralizations, and halts development to frank caries.[47]

10. Xylitol carrier:

Xylitol, a non-acidogenic sweetener, interferes with plaque formation and its adhesion to the tooth surface. It neutralizes the plaque pH by decreasing the lactic acid formation. Additionally it reduces the levels of S.mutans and assists in remineralizationof the tooth structure. It also increases the salivary flow rate and enhances protective property of saliva. This is because its concentration is higher in stimulated saliva of bicarbonate and phosphate which ends up in remineralization.[48]

Related studies:

Miake et al observed that xylitol can induce remineralization in deeper layer of demineralized enamel by facilitating calcium movement and accessibility.[49]

11. Novel hybrid chitosan/calcium phosphate microgels:

Chitosan is the deacetylated form of the natural polysaccharide-chitin. It is soluble beneath acidic condition and has excellent antimicrobial activity. The hybrid microgels formation was guided by the chitosan macromolecules which acted as a template for the calcium phosphate deposition and resulted into in situ formation of amorphous to poorly crystalline non stoichiometric hydroxyapatite. Though, it has little effect on remineralization, it has anticariogenic property because it acts as a barrier against acid penetration contributing to the demineralization inhibition as well as inhibit the discharge of phosphorous from the enamel therefore interfering with demineralization.

Related studies:

Simeonav el al, 2019 has conducted a model study and found out that the newly developed hybrid material has several advantages as remineralizing agent such as bio-adhesiveness, antimicrobial property in addition as continuous supply of calcium and phosphate ions to ensure remineralization of initial caries lesions.[50]

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12. Biomimetically modified mineral trioxide aggregate:

The remineralization efficacy of mineral trioxide aggregate (MTA) in phosphate containing stimulated body fluid is by incorporating polyacrylic acid and sodium tripolyphosphate as a biomimetic analoges of matrix protein for remineralization of carious dentin. The biomimetic analog in MTA provides potent delivery system for remineralization of dentin because of release of biomimetic material from set MTA. The presence of polyphosphate acts as a supplementary phosphate source when its availability is compromised.[51]

It could be a promising source of remineralization and widens the scope of MTA in odontology.

CONCLUSION:

The era of preventive and minimal invasive dentistry clearly dictates the necessity for developing newer approaches to remineralize enamel caries lesion. Fluoride mediate repair depends on variables such as saliva quality and patient compliance. However, non-fluoridated remineralization systemareless dependent on such factors. Furthermore, fluoride is dose -dependent and overdose can lead to fluorosis. Therefore, biomimetic strategy for enamel regeneration are the long run side to switch the demineralized tissue. With these nontoxic alternatives to remineralization method, we would be able to re-establish the oral health of oral tissue while not being beneath the danger of fluoride toxicity if ingested at high levels, particularly in children.

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