Review Article

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NEW VISTAS IN NON – FLUORIDE REMINERALIZING AGENTS: A LITERATURE REVIEW

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ABSTRACT

Dental caries is a highly prevalent chronic public health disease. The focus of modern dentistry has gradually changed from 'the cure to the prevention strategies'. Nowadays dental caries is treated as a process rather than curing the lesion only. The role of demineralization and remineralization has been better understood. There is a recent outburst of alternate non – fluoride remineralizing agents which may serve as alternative and also adjunct for preventing, arresting or even reversing dental caries. This paper reviews the various non-fluoride remineralizing agents that may hold promising results in prevention of dental caries in future. A search of articles from "PubMed" and "Medline" and databases like Google and Google scholar, ScienceDirect with the keywords dental caries, nonfluoride technologies, remineralization and demineralization was conducted, out of a total 110 articles, 72 articles have been used in the present review.

KEYWORDS: Dental caries, Remineralization, Prevention, Nonfluoride technologies.

INTRODUCTION

Owing to its globally high prevalence, dental caries is now considered as a 'pandemic' disease characterized by a high percentage of untreated carious teeth having a significant impact in terms of pain, discomfort, functional limitations and on quality of life of the individual.[1] The heart of dental caries research have always been the interventions targeted toward its prevention and control and this focus has recently shifted to the development of methodologies for the detection of the early stages of caries lesions and the non-invasive treatment of these lesions. The non-invasive treatment of early lesions by remineralisation has the potential to be a major advance in the clinical management of the disease.

REMINERALISATION

Dental caries is a multifactorial disease determined by the cumulative result of consecutive cycles of demineralization and remineralisation at the interface between the biofilm and the tooth surface.[2] Demineralization occurs at a low pH when the oral environment is under saturated with mineral ions, relative to a tooth's mineral content. The enamel crystal, which consists of carbonated apatite, is dissolved by organic acids (lactic and acetic) that are produced by the cellular action of plaque bacteria in the presence of dietary carbohydrates.[3] Remineralisation is the natural repair process for non cavitated lesions, and relies on calcium and phosphate ions assisted by fluoride to rebuild a new surface on existing crystal remnants in subsurface lesions remaining after demineralization. These remineralized crystals are less acid soluble than the original mineral.[3] Demineralisation and remineralisation occur

many times during the day and it is the balance between these two processes over time that influences whether a caries lesion will progress, reverse or stay the same.[4] Strategies to prevent caries should aim to limit exposure to demineralising factors, where possible, and also to promote remineralisation.[5]

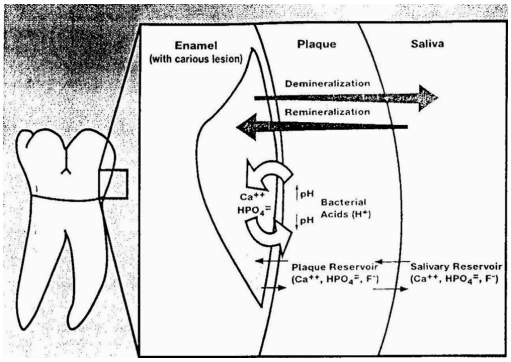

Figure 1: Cycle of demineralization and remineralization in enamel.[3]

For remineralization of enamel to occur the following six_conditions or events must occur at the same time[6]:

1. Sufficient mineral must be present in the saliva.
2. A molecule of carbonic acid must be produced.
3. The carbonic acid molecule must be produced in proximity to a mineral molecule.
4. This all has to occur in proximity to a demineralized spot in the hydroxyapatite (HAP) latticework.
5. That spot of the tooth has to be clean, so that the mineral deficient spot is accessible.
6. The carbonic acid must convert to carbon dioxide and water before any of the above circumstances change.

WHY TO GO FOR NONFLUORIDE STRATEGIES?

1. Fluoride is highly effective on smooth-surface caries, but its effect is limited on pit and fissure caries.[7-8]
2. For every two fluoride ions, 10 calcium ions and six phosphate ions are required to form one unit cell of fluorapatite($Ca_{10}(PO_4)_6F_2$). Hence on topical application of fluoride ions, the availability of calcium and phosphate ions can be the limiting factor for net enamel remineralization to occur and this is highly exacerbated under xerostomic conditions.[9]
3. A high-fluoride strategy cannot be followed to avoid the potential for adverse effects (e.g., fluorosis/toxicity) due to overexposure to fluoride.[7]
4. The anti-fluoride lobby which is mounting pressure poses certain legal limitations to the use of fluorides.[8]
5. Certain countries do not have fluoridated products.[8]

METHODOLOGY

The bulk of this review will deal with present day non - fluoride technologies. A search of articles from "PubMed" and "Medline" and databases like Google and Google scholar, Science Direct and Wiley with the keywords remineralization, demineralization and non - fluoridated demineralizing agents was conducted. We retrieved a total of 110 abstracts and 139 full length papers, of which 110 articles that discussed current technologies of non- fluoridated demineralizing agents were read and 72 most relevant articles were included in this paper.

NON – FLUORIDE REMINERALIZATION THERAPIES

Tricalcium phosphate (TCP)

Tricalcium phosphate has the chemical formula $Ca3\ (PO_4)_2$, and exists in two forms, alpha and beta. Typically, particles range from 0.01 to 5 microns in size.[10]When TCP comes into contact with the tooth surface and is moistened by saliva, the protective barrier breaks down making calcium, phosphate and fluoride ions available to the tooth.[11] The remineralizing ingredient of the new product Clinpro 5000 toothpaste is TCP (5000 ppm Fluoride), which consists of calcium oxides, calcium phosphate, and free phosphates.[12]

Fluoride Plus Functionalized β-TCP

*f*TCP is the resultant material derived through the coupling of β-tricalcium phosphate (β-TCP) with organic and/or inorganic moieties, such as carboxylic acids and surfactants.[13] In contrast to other calcium-based approaches, *f*TCP is a low dose system designed to fit within existing topical

fluoride preparations. The functionalization of β-TCP provides a barrier that prevents premature fluoride-calcium interactions and aids in mineralization when applied *via* common preparations and procedures. Each *f* TCP ingredient is designed to supplement fluoride to enhance fluoride-based nucleation activity, with subsequent remineralisation driven by dietary and salivary calcium and phosphate.[14] *f*TCP incorporated into a 5% NaF varnish improves the micro hardness and acid resistance.[15] Studies are currently underway to demonstrate the clinical advantages of *f* TCP in rinse form. It is used in products 3M EspeClinPro fluoride dentifrice.

Pronamel

It is a relatively new addition to the Sensodyne family of fluoride dentifrices, and is targeted to help with the problem of dental erosion. It contains 5% potassium nitrate to help relieve tooth sensitivity, has a neutral pH and a low abrasivity, and lacks the detergent sodium lauryl sulfate normally found in dentifrices. The fluoride component is sodium fluoride, giving 0.15% w/v fluoride ion, or 1500 ppm, an increase of 50% above conventional dentifrices.[16]A study was conducted which focussed on dental erosion and compared Proenamel™ and GC MI Paste/Tooth Mousse™ . Both agents reduced enamel loss and offered a degree of protection from erosion.[17]

Bioactive glass containing calcium sodium Phosphosilicate

NovaMin is one of the bioactive glass-ceramic materials, which falls into a class of newer agents that provide calcium and phosphate upon reaction. NovaMin comprises of 45% SiO_2, 24.5% Na_2O, 24.5% CaO and 6% P_2O_5.[17] The active ingredient in NovaMin is calcium sodium phosphosilicate that reacts when exposed to aqueous media and provides calcium and phosphate ions that form a hydroxy-carbonate apatite (HCA) with time.[18] Novamin adheres to exposed dentin surface and forms a mineralized layer that is mechanically strong and resistant to acid. There is continuous release of calcium over time, which maintains the protective effects on dentin.[19] The NovaMin technology was developed by Dr. Len Litkowski and Dr. Gary Hack at the Department of compositions Restorative Dentistry at the University of Maryland and by Dr. David Greenspan at NovaMin® Technologies Inc.[20] Currently available products in the market are NovaMin: SootheRx, DenShield, NuCare-Root Conditioner with NovaMin, NuCare-Prophylaxis Paste with NovaMin, and Oravive.

Amorphous calcium phosphate

The ACP technology was developed by Dr. Ming S. Tung. In 1999, ACP was incorporated into toothpaste called *Enamelon*and later reintroduced in 2004 in *Enamel Care*toothpaste by Church and Dwight.[7] Amorphous calcium phosphate (ACP) is the initial solid phase that precipitates from a highly supersaturated calcium phosphate solution, and when applied topically, it hydrolyses under physiological temperatures at a pH of 7.4 to form octacalcium phosphate and an intermediate, and then surface apatite. [16,21] This is purely a surface phenomenon, and fundamentally different from remineralisation of enamel subsurface lesions, which requires penetration of ions into the enamel surface. This surface effect would, paradoxically, reduce surface porosity and thus renders them incapable of achieving deep penetration of mineral into subsurface defects and white spot lesions.[22] This technology has its own disadvantages. The unstabilized ACP rapidly transforms to crystalline phases in the mouth and in so doing may act to promote dental calculus. In the presence of fluoride ions the unstabilized ACP may produce fluorapatite. The formation of fluorapatite intra-orally would sequester available fluoride ions thereby reducing their ability to remineralize subsurface enamel during acid challenge.[5]

It is available as Discus Dental's Nite White Bleaching Gel and Premier Dental's Enamel Pro Polishing Paste. It is also used in the Aegis product line, such as Aegis Pit and Fissure Sealant, produced by Bosworth.[7]

Dicalciumphosphate dehydrate (DCPD)

Dicalcium phosphate dehydrate (DCPD) in a dentifrice increases the levels of free calcium ions in plaque fluid, and these remain elevated for up to 12 hours after brushing, when compared to conventional silica dentifrices.[23]This material has been used in some fluoride dentifrices in attempt to enhance on the remineralizing effects of the fluoride component.[16] Calcium from DCPD was incorporated into enamel and detected in plaque

18 hours post-treatment after brushing with a DCPD dentrifice which fosters improved remineralisation of teeth in combination with fluoride.[24]

(CPP-ACP nanocomplexes): a protein technology

Casein is the predominant phosphoprotein in bovine milk present primarily as calcium phosphate stabilized in cellular complexes and accounts for almost 80% of its total protein. A group of peptides, known as casein phosphopeptides (CPP), have been shown to stabilize calcium and phosphate, preserving them in an amorphous or soluble form termed as amorphous calcium phosphate (ACP).[25]The proposed mechanism of anticariogenicity for the CPP–ACP is that it binds readily to the surface of the tooth[26], as well as to the bacteria in the plaque surrounding the tooth surface.CPP inhibits adherence of oral bacteria to saliva-coated hydroxyapatite beads (S-HA). By selectively inhibiting streptococcal adhesion to teeth, it can modulate the microbial composition of dental plaque and favour establishment of less cariogenic species such as oral actinomyces.[27] CPP-ACP deposits a high concentration of ACP in close proximity to the tooth surface. Therefore under acidic conditions, this localized CPP-ACP buffers the free calcium and phosphate ions, substantially increasing the level of calcium phosphate in plaque and maintaining a state of supersaturation that inhibits enamel demineralization and enhances remineralization.[5] This protein nanotechnology was developed by Eric Reynolds and co-workers at the University of Melbourne, and has since been incorporated into chewing gums such as Recaldent gum™ and Trident White™ and tooth crèmes (GC Tooth Mousse™ and MI Paste™). Recaldent works effectively as a remineralizing agent at acidic pH levels (down to 4.0) as well as in the neutral and alkaline range.[5,28] The material is pH responsive, with increasing pH increasing the level of bound ACP and stabilizing free calcium and phosphate, so that spontaneous precipitation of calcium phosphate does not occur. This provides an anti-calculus action.[29]One more advantage of this product is digestible by people with lactose intolerance.[6]

CPP-ACFP Nano-complexes

Casein phosphopeptides containing the cluster sequence-Ser(P)-Ser(P)-Ser(P)-Glu-Glu- bind fluoride as well as calcium and phosphate, and thus can also stabilize calcium fluoride phosphate as soluble complexes. These complexes are designated CPP-ACFP nanocomplexes.[30]The reported additive anticariogenic effect of the CPP-ACP nanocomplexes and F may be attributable to the localization of ACFP at the tooth surface by the CPP, which co-localizes calcium, phosphate and fluoride as bioavailable ions in the correct molar ratio to form fluorapatite.[5] A dentifrice formulation containing 2% CPP-ACP nanocomplexes plus 1100 ppm F has been shown to be superior (2.6 times) to a dentifrice containing only 1100 ppm F in remineralization of enamel subsurface lesions with mineral that was more resistant to acid challenge. The results indicate that the CPP is an excellent delivery vehicle to localize bioavailable calcium, fluoride and phosphate ions at the tooth surface to remineralize subsurface enamel lesions with fluorapatite.[31]

Xylitol carrier

Xylitol is one of the non-sugar alcohol sweetener that has been shown to have non - cariogenic as well as cariostatic effects. Cariogenic bacteria process xylitol very poorly, producing little acid or plaque. This decreases caries incidence and promotes colonization of less virulent strains of bacteria that can ferment xylitol. The use of chewing gum carrying xylitol increases salivary flow rate and enhances the protective properties of saliva.[32] A novel method of delivering remineralizing ions (calcium and phosphate) in combination with xylitol has been developed using a NaF varnish (Embrace Varnish, Pulpdent). This varnish contains calcium and phosphate salts that have been nano-coated with xylitol (cXp technology). The xylitol coating prevents early reaction and produces a sustained release of the remineralizing ions. Saliva exposure dissolves the xylitol and frees the calcium and phosphate ions. They then react with the fluoride in the varnish to form protective fluorapatite on the teeth.[33]

Nano-hydroxyapatite

Poorly crystalline HA nanocrystals, in addition to the excellent biological properties of HA, such as

nontoxicity and lack of inflammatory and immunizer responses, have bioresorption properties under physiological conditions. This property can be modulated by modifying its degree of crystallinity, which is achieved by the implementation of innovative synthesis with a nanosize crystals control.[34] A study was done to determine the effect of nano-hydroxyapatite concentrations on initial enamel lesions under dynamic pH-cycling conditions. It was concluded that nanohydroxyapatite had the potential to remineralize initial enamel lesions. A concentrationof 10% nano-hydroxyapatite may be optimal for remineralization of early enamel caries.[35]

The Trimetaphosphate Ion

The potential mode of action of trimetaphosphate ion (TMP) is likely to involve adsorption of the agent to the enamel surface, causing a barrier coating that is effective in preventing or retarding reactions of the crystal surface with its fluid environment, and hence reducing demineralization during acid challenge.[36]Gu highlighted the role of sodium TMP as a templating analog of dentin matrix phosphoproteins for inducing intra fibrillary remineralization of apatite nanocrystals within the collagen matrix of incompletely resin infiltrated dentin.[37]

Ion exchange resins

The ion exchange system provides a controlled release system for the anti-carious treatment of dental tissues.[6] Anna Toraddo et.al conducted an invitro study to determine the ability of a dentifrice containing a mixture of ion-exchange resins (named NMTD), which supplies calcium, fluoride, phosphate, and zinc ions, to promote remineralisation and/or inhibit demineralization of dental human enamel in a pH cycling model. They found that Inclusion of calcium and phosphate ion-exchange resins in the dentifrice containing a fluoride ion exchange resin maintained a similar net outcome of the conventional dentifrice in the demineralization/ remineralisation process under the experimental conditions employed.[38]

Calcium carbonate carrier – SensiStat

The SensiStat technology is made of arginine bicarbonate, an amino acid complex, and particles of calcium carbonate, a common abrasive in toothpaste. The arginine complex is responsible for adhering the calcium carbonate particles to the dentin or enamel surface and allows the calcium carbonate to slowly dissolve and release calcium that is then available to remineralize the tooth surface.[39] The SensiStat Technology was developed by Dr. Israel Kleinberg of New York. The technology was first incorporated intoOrtek'sProclude desensitizing prophy paste and later in Denclude.[40]

BiodentineTricalcium Silicate Cement

Biodentine (Septodont) is a new bioactive calcium silicate based product that has been designed as an all-around "dentin replacement" material. It can be used in endodontic repair (root perforations, apexification, resorptive lesions), pulp capping, as well as a dentin replacement in restorative dentistry. It was formulated by taking the MTA-based endodontic repair cement technology, improving its physical and handling properties, and creating a dentin replacement material with significant reparative qualities. Biodentine penetrates the dentinal tubules forming tag-like structures that create a micromechanical lock with the tooth. It then begins to stimulate reparative dentin. Clinical trials confirm Biodentine's ability to preserve pulp vitality even in very difficult cases.[33] Biodentine has the potential to heal pulp, avoiding what may have been inevitable endodontic treatment in the past.

Photonic conversion

Photonic conversion is a process of formation of fluorapatite, rather than calcium fluoride within dentine by application of neutral sodium fluoride gels followed immediately by laser treatment.[41]

Self assembling peptide

Peptide treatment for early caries lesion is the area of current research. Peptides significantly increase net mineral gain due to a combined effect of increased mineral gain and inhibition of mineral loss. Rationally designed β-sheet-forming peptides P114 that self assemble themselves to form three-dimensional scaffolds under defined environmental conditions have been shown to

nucleate hydroxyl apatite de novo and to have potential applications in mineralized tissue regeneration, mimicking the action of enamel matrix proteins during tooth development. Results suggest that a single application of P114 can be beneficial in the treatment of early caries lesions and that self assembling peptides are candidate materials for mineralized tissue regeneration and repair.[42] P114 is safe, non-invasive and acceptable to patients. The treatment differs from other 'filling without drilling'. The use of a biomimetic peptide such as P114 has the additional advantage of effecting 'natural' repair by regenerating the mineral itself. P114 is a well-tolerated treatment, and currently designed to test 'next generation' peptides to accelerate the repair process, thus making 'filling without drilling' a reality.[43]

Grape Seed Extract

Polyphenols are plant-derived substances that have antioxidant and anti-inflammatory properties.[44, 45] They interact with microbial membrane proteins, enzymes and lipids, thereby altering cell permeability and permitting the loss of proteins, ions and macromolecules. One such polyphenol is proanthocyanidin (PA), which is a bioflavanoid-containing benzene-pyran-phenolic acid molecular nucleus.[45] The PA accelerates the conversion of soluble collagen to insoluble collagen during development and increases collagen synthesis.[44] Grape seed extract (GSE) has a high PA content. PA-treated collagen matrices are non-toxic and inhibit the enzymatic activity of glucosyl transferase, F-ATPase and amylase. glucosyl transferases, which are produced by S. mutans that polymerize the glucosyl moiety from sucrose and starch carbohydrates into glucans and in turn inhibits caries.[44]

Ozone therapy

Ozone is a powerful oxidizing & antimicrobial agent with numerous advantages in modern dentistry which includes non invasive treatment of initial caries by remineralization; root caries; as intracanal irrigant; treatment of alveolitis, avascular osteonecrosis of jaw; anti-plaque agent; as adjunct in periodontal surgical & maintenance phase; for disinfection of implant surface; to treat peri-implantitis.[46] It achieves its antimicrobial activity against caries because ga seous/aqueous form of ozone eliminates cariogenic bacteria by decarboxylation of pyruvic acid which is produced by acidogenic bacteria to acetic acid. This acetic acid not only results in remineralization of carious lesions; it also buffers plaque due to high pKa values. Treatment with ozone results in more reversal of noncavitated lesions than cavitated lesions. Application of ozone is capable of clinically reversing root caries too.

Electrically Accelerated and Enhanced Remineralisation (EAER)

Professor Nigel Pitts and Dr Chris Longbottom devised a technology through which the early to medium tooth decay can undergo self-healing. Iontophoresis was used in which the inside of the tooth is turned into the electrode, which drive minerals into the most damaged areas leading to rebuild of the tooth from inside. This process takes 15 minutes. It's done with a "healing hand piece" which is the size of a highlighter pen. It can be carried out by a dentist or a hygienist, depending on the local regulations.[47]

Resin Infiltration

Resin infiltration technique is a novel technology that seems to bridge the gap between noninvasive and minimally invasive treatment. The concept of caries infiltration was first developed at the Charité Berlin and the University of Kiel as a micro-invasive approach for the management of smooth surface and proximal non-cavitated caries lesions.[48] The principal of resin infiltration is to perfuse the porous enamel with resin by capillary action. This aims to arrest lesion progression by occluding the microporosities that provide diffusion pathways for the acids and dissolved materials.[49] It is marketed under the name Icon® (DMG America Company, Englewood, NJ).[48]

CONCLUSION

Remineralization of lesions should not be incorporated as a stratagem but as a philosophy of dentistry. With a clearer understanding of the implementation of these remineralizing agents and new technologies accessible to us, we can create a more favourable relationship in which remineralization occurs more often than demineralization.

REFERENCES

1. Edelstein BL. The dental caries pandemic and disparities problem. BMC Oral Health 2006; 6(Suppl 1):S2.
2. Fejerskow O, Kidd, EA, Nyvad B, Baclum V, Defining the disease: an introduction: in Fejerskov O, KiddE (eds): Dental Caries- The Disease and its Clinical Magement, ed 2, Oxford, Blackwell Munksgaard, 2008, p 3-6.
3. Featherstone JD. Dental caries: a dynamic disease process. Aust Dent J. 2008; 53(3):286-91.
4. Selwitz RH, Ismail AI, Pitts NB. Dental caries. Lancet 2007; 369(9555):51–9.
5. Reynolds EC. Calcium phosphate-based remineralization systems: scientific evidence? Aust Dent J 2008;53(3):268–73.
6. Pradeep K, Kumar PR. Remineralizing agents in the non-invasive treatment of early carious lesions. Int J Dent Case Rep 2011; 1:73-84.
7. Goswami M, Saha S, Chaitra TR. Latest developments in non-fluoridated remineralizing technologies. J Indian Soc Pedod Prev Dent 2012; 30:2-6.
8. Chhabra KG, Shetty PJ, Prasad KVV, Mendon CS, Kalyanpur R. The beyond measures: Non flouride preventive measures for dental caries. J Int Oral Health 2011; 3:1-8.
9. Reynolds EC. Calcium phosphate-based remineralization systems: scientific evidence?.Aust Dent J 2008; 53(3):268–73.
10. Döri F, Arweiler N, Gera I, Sculean A. Clinical evaluation of an enamel matrix protein derivative combined with either a natural bone mineral or beta-tricalcium phosphate. J Periodontol. 2005; 76(12):2236-43.
11. Rirattanapong P, Vongsavan K, Tepvichaisillapakul M. Effect of five different dental products on surface hardness of enamel exposed to chlorinated water in vitro. Southeast Asian J Trop Med Public Health 2011; 42:1293-8.
12. Su N, Marek CL, Ching V, Grushka M. Caries prevention for patients with dry mouth. J Can Dent Assoc 2011; 77:b85.
13. Karlinsey RL, Mackey AC. Solid-state preparation and dental application of an organically-modified calcium phosphate. J Mater Sci 2009; 44:346-349.
14. Karlinsey RL, Pfarrer A.M. Fluoride Plus Functionalized β-TCP:A Promising Combination for Robust Remineralization.Adv Dent Res 2012; 24(2):48-52.
15. Flanigan PJ, Vang F and Pfarrer AM, Remineralization and Acid Resistance Effects of 5% NaF Varnishes, J dent Res 89 (Spec Iss B), 383, 2010.
16. Walsh LJ. Contemporary technologies for remineralization therapies: A review. Int Dent SA 2009;11:6-16.
17. Rees J, Loyn T, Chadwick B. Pronamel and tooth mousse: an initial assessment of erosion prevention in vitro. J Dent. 2007;35(4):355-7.
18. NovaMin Research Report. Clinical study of NovaMin-containing dentifrice's ability to produce consumer noticeable whitening and brightening effects. Research Institution:Hill Top Research, Cincinnati, OH. http://www.novamin.com/pdf/research_reports/NRR4-whitening-bright.pdf (accessed on Oct 2nd 2016).
19. Burwell A, Jennings D, Muscle D, Greenspan DC. Novamin and dentin hypersensitivity- invitro evidence of efficacy. J Clin Dent 2010;21:66-71.
20. Burwell AK, L.Litkowski,D.Greenspan.Calcium Sodium Phosphosilicate (NovaMin®): Remineralization potential Adv. Dent. Res. 2009;21: 83-86.
21. Jie Zhao, Yu Liu, Wei-bin Sun, Hai Zhang. Amorphous calcium phosphate and its application in dentistry. Chem Cent J. 2011; 5: 40.
22. Tung MS, Eichmiller FC. Dental applications of amorphous calcium phosphates. J ClinDent. 1999;10 (1Spec No):1 -6.
23. Sullivan RJ, Charig A, Haskins JP, Zhang YP, Miller SM, Strannick M, *et al*. *In vivo* detection of calcium from

dicalcium phosphate dihydratedentrifrice in demineralized human enamel and plaque. Adv Dent Res 1997;11:380-7.

24. Wefel JS, Harless JD. The use of saturated DCPD in remineralization of artificial caries lesions *in vitro*. J Dent Res 1987;66:1640-3.
25. Cochrane NJ, Saranathan S, Cai F, Cross KJ, Reynolds EC.Enamel subsurface lesion remineralisation with casein phosphopeptide stabilised solutions of calcium, phosphate and fluoride. Caries Res 2008;42:88–97.
26. Reynolds EC, Black CL, Cai F. Advances in enamel remineralization: anticariogenic casein phosphopeptide – amorphous calcium phosphate. J Clin Dent 1999;10:86–88.
27. Kumar VL, Itthagarun A, King NM. The effect of casein phosphopeptides-amorphous calcium phosphate on remineralization of artificial caries – lesions: An *in vitro* study. Aust Dent J 2008;53:34-40.
28. Cross KJ, Huq NL, Palamara JE, Perich JW, Reynolds EC.Physicochemical characterization of casein phosphopeptide-amorphous calcium phosphate nanocomplexes. J Biol Chem. 2005;280(15):15362-9.
29. Reynolds EC. Anticariogenic complexes of amorphous calcium phosphate stabilized by casein phosphopeptides: a review. Spec Care Dentist. 1998;18(1):8-16.-84
30. Cross KJ, Huq NL, Stanton DP, Sum M, Reynolds EC. NMR studies of a novel calcium, phosphate and fluoride delivery vehicle-alpha(S1)-casein(59-79) by stabilized amorphous calcium fluoride phosphate nanocomplexes. Biomaterials. 2004;25(20):5061-9.
31. Reynolds EC, Cai F, Cochrane NJ, et al. Fluoride and casein phosphopeptide-amorphous calcium phosphate. J Dent Res 2008;87:344–348.
32. Makinen KK. Sugar alcohols, caries incidence and remineralization of caries lesions: A literature review. Int J Dent 2010;2010:981072.
33. Fay Goldstep. Dental Remineralization: Simplified.[Internet] http://www.oral healthgroup.com/[llast accessed on 2016 Sep 22]
34. Roveri N, Battistella E, Bianchi CL, *et al*., "Surface Enamel Remineralization: Biomimetic Apatite Nanocrystals and Fluoride Ions Different Effects," Journal of Nanomaterials 2009, Article ID 746383 doi:10.1155/2009/746383.
35. Huang SB, Gao SS, Yu HY. Effect of nano-hydroxyapatite concentration on remineralization of initial enamel lesion *in vitro*. Biomed Mater 2009;4:55-9
36. Gonzalez M. Effect of Trimetaphosphate Ions on the processof Mineralization. J Dent Res 1971;50:1055-60.29.
37. Gu LS, Kim J, Kim YK, Liu Y, Dickens SH, Pashley DH, *et al*. A chemical phosphorylation-inspired design for Type I collagen biomimetic remineralization. Dent Mater 2010;26:1077-89.
38. TorradoA, Valiente M, Zhang W, et. al. Remineralizat ion Potential of a New Toothpaste Formulat ion: An In-Vitro Study. J Contemp Dent Pract 2004 ;(5)1:018-030.
39. Nizel AE, Harris RS. The Effects of Phosphates on Experimental Dental Caries: A Literature Review. J Dent Res 1964; 43:1123-35.
40. McClure MJ. Further studies on the cariostatic effect of organic and inorganic phosphates. J Dent Res 1963;42:693-9.
41. Vlacic J, Meyers IA, Walsh LJ. Photonic conversion of hydroxyapapite to fluorapatite: a possible mechanism for laser-activated fluoride therapy. J Oral Laser Appl. 2008;8(2): 95-102
42. Thompson A, Grant LP, Tanzer JM (1999) Model for assessment of carious lesion remineralization, and remineralization by a novel toothpaste. J Clin Dent 10: 34-39
43. Walsh LJ (2007) Tooth Mouse: Anthology of applications. GCAsiaPte Ltd, Singapore.
44. Xie Q, Bedran-Russo AK, Wu CD. In vitro remineralisation effects of grape

seed extract on artificial root caries. J Dent 2008; 36:900-6.

45. Ferrazzano GF, Amato I, Ingenito A, Zarrelli A, Pinto G, Pollio A. Plant polyphenols and their anti-cariogenic properties: A review. Molecules 2011;16:1486-507
46. Rudrakshi C, MLV Prabhuji. Ozone therapy in dentistry. J Indian Dent Assoc; September 2014; 8(9).
47. Bridget C. Renaissance and remineralisation. RDH 2015:88-90.
48. Kugel G, Arsenault P, Papas A. Treatment modalities for caries management, including a new resin infiltration system. Compend Contin Educ Dent.2009;30(3):1- 10
49. Meyer-Lueckel H, Paris S. Progression of artificial enamel caries lesions after infiltration with experimental light curing resins. Caries res. 2008; 42(2):117-124.