RESEARCH ARTICLE

ROLE OF FLUORIDE IN DENTAL CARIES RE-MINERALIZATION: A REVIEW

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Manuscript Info	*Abstract*
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Traditional management of dental caries has focused primarily on treatment via the excision of diseased tissues and subsequent restoration of the defect (Tsang et al., 2006). [1] Mechanical tooth preparation is a destructive and irreversible method of removing the natural dental tissues. The artificial dental materials closely resemble those of natural dental tissues are in use now a days for dental caries refilling. Dental restorations and even implants cannot replace natural teeth completely (Stewart and Hale 2003). [2] Dental caries is a disease that involves the localized chemical dissolution of dental hard tissues due to acids produced by plaque bacteria in bio-film that covers the affected area (Fejerskov, 2008).[3] A comprehensive treatment plan for dental caries should include, elimination of cariogenic bacteria, reducing plaque acidogenicity, enhancing tooth remineralisation, and repairing the damaged teeth. Contemporary caries management philosophy has changed from the traditional surgical approach to a medical model, which often includes dietary analysis and advice, oral hygiene instruction, placement of fissure sealants, and the use of fluoride therapy, xylitol chewing gum, and antimicrobial agents such as chlorhexidine. Various forms of fluoride therapy are used to prevent and sometimes to arrest caries, although the effects of fluoride therapy are related to the chemical composition of the fluoride product and the method used to apply the material to the tooth surface (Chu, 2007).[4].

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Introduction:-

Traditional management of dental caries has focused primarily on treatment via the excision of diseased tissues and subsequent restoration of the defect (Tsang et al., 2006). [1] Mechanical tooth preparation is a destructive and irreversible method of removing the natural dental tissues. The artificial dental materials closely resemble those of natural dental tissues are in use now a days for dental caries refilling. Dental restorations and even implants cannot replace natural teeth completely (Stewart and Hale 2003). [2] Dental caries is a disease that involves the localized chemical dissolution of dental hard tissues due to acids produced by plaque bacteria in bio-film that covers the affected area (Fejerskov, 2008).[3] A comprehensive treatment plan for dental caries should include, elimination of cariogenic bacteria, reducing plaque acidogenicity, enhancing tooth remineralisation, and repairing the damaged teeth. Contemporary caries management philosophy has changed from the traditional surgical approach to a medical model, which often includes dietary analysis and advice, oral hygiene instruction, placement of fissure sealants, and

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Mechanism of action of fluoride:
Although fluoride's specific mechanism of action in caries prevention is not fully understood, it is generally accepted that fluorides applied topically or taken systemically have an effect on tooth surfaces. Shellis and Duckworth reported that fluoride acts topically to prevent dental caries (Shellis and Duckworth, 1994).[5] Fluoride inhibits plaque metabolism, alters plaque composition, affects plaque formation, and reduces the plaque bacteria's ability to produce large amounts of acid from carbohydrates (Shellis and Duckworth, 1994).[5] Fluoride also inhibits enamel demineralization. The calcium fluoride that is deposited on a tooth surface after fluoride therapy is not readily soluble and can act as a fluoride reservoir. This fluoride also can lower the critical pH value of hydroxyapatite crystal dissolution (the pH value at the time that demineralization occurs) from approximately 5.5 to 4.5 in the mouth. In addition, fluoride can be incorporated incrementally into fluroapatite crystals on the tooth surface, making the surface more resistant to acid dissolution. In addition to inhibiting demineralization, fluoride enhances enamel remineralisation, increasing the speed of the remineralisation process and the mineral content of early carious lesions. The incorporation of fluoride also makes the deposited mineral less acid-soluble.

Requirements of an ideal re-mineralization bioactive agent:
1. Diffuses into the subsurface, or delivers calcium and phosphate into the subsurface.
2. Does not deliver an excess of calcium.
3. Does not favour calculus formation.
4. Works at an acidic pH.
5. Works in xerostomic patients.
6. Boosts the remineralizing properties of saliva.
7. For novel materials, shows a benefit over fluoride

Fluoride compounds used in dentistry as common fluoride delivery system

Delivery system	Fluoride concentration (ppm)
Water fluoridation	0.5 to 1.0
Fluoridated Salt	250
Fluoridated Milk	2.5 -5.0
Fluoride drop, tablets, chewing gum	0.25mg per drop, tablets, pellet
Fluoride mouthrinse	200 (daily), 900 (weekly)
Fluoride toothpaste	2500-600 (children), 1000-1500(adult)
Fluoride tooth mousse	1100 (0.11% NaF)
Fluoride gel	1000 (0.4%SnF_2) -20000(2% NaF)
APF gel/foam	12300 (1.23%NaF)
Fluoride solution	4840 (2%SnF_2) - 19360 (8%SnF_2)
Fluoride Varnish	22600 (5%NaF)
Silver diamine fluoride solution	44,800 (38% Ag $(NH_3)_2F$)

The common fluoride compounds used in topical fluoride agents include sodium fluoride (NaF), which can be acidulated and buffered with a phosphate to form acidulated phosphate fluoride (APF); sodium monofluorophosphate (MFP) (Na2FPO3); and stannous fluoride (SnF2). Hexafluorosilicic acid (H2SiF6) and sodium silicofluoride (Na2SiF6) are used commonly in water fluoridation. Dental researchers are investigating other fluoride compounds, such as silver diamine fluoride (Ag(NH3)2F) and titanium tetrafluoride (TiF4) for controlling caries. Common methods for delivering fluoride include water fluoridation, fluoridated salt, fluoridated milk, fluoride toothpaste, fluoride supplements (in the form of a drop or tablet), fluoride chewing gum, fluoride solution, fluoride mouthwash, fluoride gel, fluoride foam, fluoride mousse, and fluoride varnish. The fluoride concentration or content in the delivery systems that are intended for systemic absorption usually is much lower than that found in systems intended for topical application. Few other chemical entities can be delivered in such a flexible manner to provide such important benefits. However, fluoride's ability to control caries depends on whether the fluoride is available in the oral cavity at concentrations that can significantly affect the ongoing demineralization and remineralisation process (Ellwood et al., 2008).[6] Since the cariostatic mechanism of fluoride is mainly topical, a

good fluoride delivery system should provide a substantial topical application of fluoride and ensure that a minimal amount of fluoride is ingested; ideally, the system should be cost-effective as well.

Water fluoridation:
Water fluoridation is defined as the controlled addition of a fluoride compound to a public water supply in order to reduce dental caries (Recommendations for using fluoride to prevent and control dental caries in the United States, 2001).[7] Sodium fluoride, hexafluorosilicic acid, and sodium silicofluoride are common fluoride compounds added to the water supply because of their solubility, safety, availability, and low cost. Water fluoridation provides a low concentration of and frequent intraoral exposure to fluoride. The recommended optimal fluoride concentration in water is temperature-related, ranging from 0.5–1.0 ppm for different regions of the world (WHO, 1994).[8] The FDI World Dental Federation concluded that fluoridation of water supplies remains the most effective public health measure for preventing dental caries (FDI statement, 2009).[9] Despite the success of drinking water fluoridation in preventing dental caries in various population groups, concerns about ethics, safety, and efficacy have made it a controversial topic.

Fluoridated salt:
First used in Switzerland in 1955, fluoridated salt uses the same public health principle for caries control as water fluoridation. Potassium fluoride or sodium fluoride is added to the salt, usually in a fluoride concentration of 250 ppm (based on adult consumption of approximately 10 g of salt per day) (Marthaler and Petersen, 2005).[10] Fluoridated salt is well-accepted by the Swiss communities, offering consumers a fluoride option that is not available to communities with fluoridated water and a meal prepared with 250 ppm fluoridated salt significantly increased the salivary fluoride level for approximately 30 minutes (Hedman et al., 2006). [11]

Fluoridated milk:
Typically, fluoride has been added in milk at 2.5–5.0 ppm (Pakhomov et al., 1995 and Bian et al., 2003). [12, 13] Fluoridated milk has been available to children through public school milk programs or national nutritional programs. Such programs are intended to target the oral health of young children, and theoretically should be more efficient than water fluoridation. Parents can choose between fluoridated or non-fluoridated milk for their children. According to Burt and Eklund, many studies that investigated the efficacy of fluoridated milk were seriously flawed (Burt and Eklund, 2005). [14] Fluoride is incompletely ionized in milk; as a result, limited topical effect can take place. There are also other concerns, such as the considerable proportion of children who do not drink milk for one reason or another (Stamm, 1972).[15] Although the distribution of fluoridated milk through school milk or national nutritional programs can offer a convenient and cost-efficient means of targeted fluoride supplementation, a 2005 Cochrane review concluded that there are an insufficient number of good quality studies to provide evidence that fluoridated milk offers sufficient protection against caries (Yeung et al., 2005). [16]

Fluoride supplements:
Fluoride drops or tablets are used as a supplement to water fluoridation or as an alternative method in areas where fluoridated water is not available. The ADA approved a fluoride supplement dosage schedule in 1994 (see Table 2). According to Ellwood et al, fluoride drops or tablets help to maintain levels of fluoride in the oral fluids that prevent the development of caries. A 1998 study by Hu et al reported on preschool children in a fluoride deficient area who received fluoride drops daily and developed less caries compared to a control group (Hu et al., 1998). [17] Fluoride tablets (sometimes taken in combination with vitamins) can be chewed and swallowed or dissolved in water to form a drink. A reduction in caries was observed when fluoride tablets were used in 1,237 12-year-old children (Momeni et al., 2007). [18] Another two year study did not support a self-administered regimen of fluoride lozenges for caries prevention (Stecksen-Blicks et al., 2008). [19] This study followed 160 high caries risk children (10–12 years of age) who took 1.5 mg fluoride (via tablets) every day. The children did not show significant caries reduction compared to the control group (Stecksen- Blicks et al., 2008). [19] Ellwood et al reviewed the fluoride delivery system and concluded that fluoride drops and tablets are the least efficient method for delivering topical fluoride; in addition, each method inevitably results in a high level of fluoride ingestion when swallowed (Ellwood et al., 2008).[6] There is also increasing evidence that the effect of fluoride is mainly the result of chemical reactions on the tooth surface. Most European scientific dental associations no longer recommend the use of fluoride supplements, such as fluoride tablets or drops, as a standard procedure in caries prevention (Zimmer et al., 2003). [20]

Daily Fluoride supplement doses (American Academy of Pediatrics 1994)

Age (in years)   Concentration of fluoride in drinking water (ppm F)

<0.5	0.00mg
0.5-3	0.25mg
3-6	0.5mg
6-16	1.0 mg

Fluoride chewing gum:
Initially, chewing gum containing fluoride was intended for people with rampant caries and for children living in areas where water is not fluoridated (Imfeld, 1999). [21] Most of the chewing gums contain 0.25 mg fluoride per pellet. The fluoride is readily released and increases fluoride content in saliva within the first 30 minutes (Bijella et al., 2005).[22] A 1989 study revealed that chewing gum containing fluoride led to enhanced remineralization (Hattab et al., 1989).[23] More recently, Oztas et al demonstrated that this type of gum was favorable for plaque pH recovery and increased salivary fluoride concentration after a sucrose rinse (Oztas et al., 2004). [24] A 2008 review by Ly et al concluded that chewing gum with fluoride could reduce the prevalence of tooth decay (Ly et al., 2008). [25]

Fluoride toothpastes:
Among all of the topical fluoride delivery systems in use, fluoride toothpaste has been assessed most comprehensively (FDI statement, 2009).[9] The efficacy of fluoride toothpastes is well documented, and toothpastes with different fluoride compounds appear to have a similar effect in decreasing the prevalence of dental caries (Brambilla, 2001).[26] In countries where toothpaste use is widespread, fluoride toothpastes are probably the most important method for the topical application of fluoride. Sodium fluoride, acidulated phosphate fluoride, stannous fluoride, sodium MFP, and amine fluoride are among the compounds that have been incorporated into toothpaste ((WHO (1994). [8] The most common concentration of fluoride used in toothpaste is 1,000 ppm, although toothpastes for adults may include concentrations of 1,500 ppm or more (low-fluoride toothpastes containing 250–500 ppm fluoride are available for children). A 2002 Cochrane review concluded that fluoride toothpaste had a preventive fraction (that is, the difference in caries increments between the treatment and control group, expressed as a percentage of the increment in the control group) of 24% (Marinho et al., 2002). [27] The review also noted that its effectiveness at reducing caries increased among those patients at higher caries risk, those whose toothpaste had a higher fluoride content, those who used fluoride toothpaste more frequently, and young children who performed supervised brushing. However, its effectiveness is not affected by water fluoridation.

Fluoride solutions:
A 1958 study reported that stannous fluoride solutions of 2% (4,840 ppm fluoride), 4%, and 8% reduced the development of new caries by 50%over a two-year period (Muhler,1958).[28] Fluoride solutions were popular in general dental practice until a 3-year-old child died after ingesting 45 mL of stannous fluoride in a dental clinic (McFadden,1979).[29] Since then, concentrated stannous and sodium fluoride solutions have not been commonly used in the U.S. because of safety concerns. Another concentrated fluoride solution, 40% silver fluoride (AgF) solution (59,800 ppm fluoride), was used in Australia to successfully arrest caries development (Chu and Lo, 2008a). [30] Various concentrations of silver diamine fluoride (SDF) solution are available in China, Japan, and some parts of South America. According to the literature, 38% SDF (44,800 ppm fluoride) is effective in preventing new caries and arresting active caries in children (Chu et al., 2002; and Llodra et al., 2005).[31,32] Carious lesions arrested after SDF treatment are stained black, which can cause concern for the children and their parents; however, the low cost and simplicity of SDF treatment makes it a useful method for controlling prevalent early childhood caries, especially in disadvantaged communities (Chu and Lo, 2007). [4] A recent systemic review concluded that SDF may be a valuable caries preventive agent; in addition, it appears to meet the criteria of both the World Health Organization (WHO) Millennium Goals and the U.S. Institute of Medicine for 21st century medical care (Rosenblatt et al., 2009).[33] Other fluoride compound solutions have been investigated; recent laboratory studies have suggested that titanium tetra-fluoride (TiF4) solution can be an effective caries control agent (Exterkate et al., 2007; and Magalhaes et al., 2008).[34,35] However, clinical studies are necessary before this solution can be used in dental care.

Fluoride mouthwash:
Fluoride solution in a lower concentration is available as a mouthwash, which can provide direct topical exposure while minimizing systemic uptake by ingestion. These rinses have an excellent risk-benefit profile when used correctly (usually in doses of 10 mL, swished between the teeth and around the mouth for one minute) (WHO (1994). [8] Such mouthwashes generally are not recommended for children under the age of 6, as they may swallow most of the mouthwashes, resulting in unwanted systemic side effects (FDI statement, 2009). [9] Sodium fluoride mouthwash is commonly formulated at 0.05% (226 ppm fluoride) for daily home use or at 0.2% (900 ppm fluoride)

for weekly use (usually administered in supervised school oral health programs). Clinical studies have compared the daily and weekly regimens; a 1991 review of the clinical trials found that both regimens could reduce new caries development by approximately 30% (Kawall et al., 1981; Driscoll, et al.,1982 and Ripa, 1991). [36,37,38] A 2002 Cochrane review suggested that the supervised regular use of fluoride mouthwash (at concentrations of 0.05% and 0.2%) is associated with a clear reduction in caries among children (Marinho et al., 2002 [39] In populations with a caries increment of 0.25 decayed, missing, and filled surfaces (DMFS) per year, 16 children will need to use a fluoride mouthwash (rather than a non-fluoride rinse) to reduce one DMFS; in populations with a higher caries increment of 2.14 DMFS per year, two children will need to rinse to reduce one DMFS. The FDI World Dental Federation has stated that fluoride mouthwash may be an effective measure for at-risk individuals and populations (FDI statement, 2009).[9]

Fluoride gels:
Fluoride gels have a relatively high viscosity, which makes them easy to handle. Fluoride gels typically are applied to children's teeth twice a year to prevent dental caries, but they may be used more frequently when more severe caries is present. Common preparations contain 2% sodium fluoride or 0.4% stannous fluoride. The 0.4% stannous fluoride gel contains 1,000 ppm fluoride (the same concentration used in toothpaste) and can be prescribed for home use. Because fluoride uptake by enamel is enhanced by an acidic environment, fluoride gel may be acidified to form an APF gel (Brudevold et al., 1963).[40] A common APF gel mixes a 0.1% orthophosphoric acid with a 1.23% sodium fluoride that has been buffered with phosphate ions. APF gel can also be formulated by using certain gelling bases to make it thixotropic, so that the gel tends to flow under pressure but will remain viscous otherwise. This thixotropic property allows the gel to remain in the tray without running, while it thins out to penetrate pits and fissures under biting pressure. APF gel should not be used on patients with glass ionomer or porcelain restorations because the acid will etch and damage the restorations. Some fluoride gel manufacturers claim that their product can be applied to teeth for one minute; however, according to the literature, four minutes is the optimal time for treatment (Wei,1988).[41] A 2003 Cochrane review examined 14 clinical trials and found that fluoride gels reduced caries by 21% on average (Marinho et al., 2003a).[42] The FDI World Dental Federation has recommended fluoride gels for individuals at high risk for caries, although they should be used with care because of their high fluoride concentration (FDI statement, 2009).[9]

Fluoride foams:
Fluoride gel contains approximately 10 times more fluoride by weight than adult fluoride toothpaste (12,300 ppm instead of 1,450 ppm). APF foam was developed in the 1990s to reduce the potential risk of young children ingesting excessive amounts of fluoride following gel application. This foam has the same fluoride concentration (1.23%, or 12,300 ppm) and pH (3–4) as APF gel but requires approximately 20% of the quantity by weight to cover a dental arch adequately. Due to its flowable consistency, the foam can provide coverage to all tooth surfaces, especially the proximal areas. Foams are unlikely to overflow while in the applicator tray, which reduces the risk of gagging or fluoride ingestion. A clinical study found that applying APF foam biannually to the dentition of 392 preschool children reduced caries by 24% after two years. Proximal tooth surfaces were affected most (Jiang et al., 2005). [43]

Fluoride varnish:
Fluoride varnish is one of the most concentrated fluoride products available commercially. Most fluoride varnishes contain 5% NaF (22,600 ppm fluoride) in a natural colophony base, which allows the varnish to adhere to tooth surfaces in the presence of saliva (Chu, and Lo, 2008b).[44] Fluoride varnish can be applied quickly and easily. It sets rapidly on tooth surfaces so that gagging and swallowing are minimized. Its bland flavour means that it is well-tolerated by children as young as one year of age; as a caries preventive agent, there is evidence that it is as effective as APF foam (Evans, 2007). [45] However, compared to APF foam (which requires children to bite into trays for four minutes), fluoride varnish appears to be the easier method of caries prevention for both the dentist and the child. The FDI World Dental Federation also recommends fluoride varnish for individuals at risk for caries. The simplicity and acceptability of fluoride varnish also make it an appropriate caries prevention treatment for special needs populations (Chu and Lo, 2006).[46] A 2003 Cochrane review of nine clinical trials involving the use of fluoride varnishes on children and adolescents found a preventive fraction of 46% in permanent teeth and 33% in primary teeth (Marinho et al., 2003b).[47] Furthermore, the review found no relationship between the effectiveness of fluoride varnishes and the baseline caries level or the level of fluoride in the water supply (Chu and Lo, 2006). [46]

Safety of use of fluoride:

A number of studies have reported a dose-response relationship between dental caries reduction and the concentration and frequency of fluoride use (Chu and Lo, 2006). [46] However, a high concentration of fluoride can result in dental fluorosis or toxicity. There is an increased risk of developing mild forms of dental fluorosis when fluorides are used by young children. The risk of young children developing dental caries must be assessed before fluorides are administered for caries prevention. Professionally applied fluoride treatments typically are administered to children or to adults who demonstrate either caries activity or a moderate to high risk of developing caries. The toxicity of fluoride depends on the rate and amount of ingestion, the duration of exposure, and the patient's weight and age. Continuous exposure to high levels of fluoride may result in chronic toxicity, while a single excessive intake of a large amount of fluoride can lead to acute toxicity. Enamel mottling and crippling skeletal fluorosis are the first signs of chronic fluoride overdose. Acute fluoride overdose may be associated with such systemic signs and symptoms as nausea, vomiting, diarrhoea, abdominal pain and cramps, weak pulse, hypotension, pallor, paresthesia, paresis, tetany, central nervous system depression, or coma; serious cases of acute toxicity may prove fatal. The risk of developing toxicity is expressed as a probable toxic dose, the minimum dose that can cause toxic signs and symptoms. A 1992 study by Whitford reported gastrointestinal symptoms in young children and very frail adults following the ingestion of 3–5 mg F/kg, leading the author to conclude that the probable toxic dose of fluoride is 5 mg F/kg of body weight (Whitford, 1992).[48] Because home use topical fluoride agents have a very low fluoride concentration, large amounts must be consumed before a patient can reach the probable toxic dose. A 4-year-old child with an average weight of 15 kg needs to ingest more than four tubes of children's toothpaste (45g/tube; 400 ppm fluoride) to surpass the probable toxic dose of 75 mg fluoride. However, an average 4-year-old child needs to ingest only 85% of a tube of adult toothpaste (90g/tube; 400 ppm fluoride) to surpass the probable toxic dose, suggesting that adult toothpastes should be placed out of reach of young children. The estimated level of fluoride that can cause acute toxicity is 32–64 mg/kg body weight (Wei and Hattab, 1988). [49] According to the ADA's Council of Dental Therapeutics, children weighing 22 lb (10 kg) or less should receive no more than 264 mg of sodium fluoride (120 mg fluoride) at any one time to prevent accidental poisoning (Wei and Hattab, 1988).[49] Fluoride exposure is available from multiple sources. Foods usually contribute only 0.3–0.6 mg of the daily intake of fluoride (Fein and Cerklewski, 2001). [50] Fluoride is present to some extent in all foods and water; as a result, people cannot avoid ingesting some fluoride every day. In recent years, fluoride has become more available via a variety of fluoridated sources, including foods, beverages, water, toothpaste, mouthwashes, and so forth. This increased presence may account for the recent decline in dental caries globally; however, it can also increase the risk of the milder forms of dental fluorosis. The FDI World Dental Federation has proposed a coordinated approach to fluoride delivery (FDI statement, 2009). [9] It is imperative that dentists are aware of fluoride availability from all sources before embarking on a specific course of fluoride treatment. The FDI World Dental Federation states that a vast amount of scientific evidence clearly indicates that fluoride is safe and effective as long as it is used properly and at concentrations appropriate for the prevention of dental decay. Fluorosis can result when excessive fluoride is ingested during the pre-eruptive development of teeth. In the authors' experience, when fluoride is used at optimal levels for caries prevention, dental fluorosis appears in only a relatively small proportion of the population, and this side effect is often very mild.

Reasons to seek alternatives to fluorides for prevention of dental caries:

The first set of theories concerning the mechanism of action of fluoride was based exclusively on its pre eruptive effect. Arnold in 1957, was the first author to mention the post eruptive effect of fluoride in the drinking water and the ability of topical fluoride to reduce the incidence of caries (Azarpazhooh et al., 2008; Naveena et al., 2014 and Cross et al., 2007). [51, 52, 53] The mechanism by which fluoride increases caries resistance may arise from both systemic and topical applications from fluoride and can be broadly grouped as follows- increased enamel resistance, increased rate of maturation, remineralisation of incipient caries, interference with micro- organisms and improved tooth morphology (Cross et al. 2007 and Garg et al. 2015). [53, 54] However certain limitations and side effects are also associated with the systemic and topical use of fluorides if not administered in monitored dose which are listed as follows- (Preventive and community dentistry, Soben Peter, 4th edition). [55]

1. Fluoride is highly effective on smooth surface caries; its effects seem to be more limited on pit and fissure caries.
2. Fluoride is often called as a double-edged sword. This is because recommended and monitored ingestion of fluoride is associated with prevention of dental caries and an excessive intake of fluoride can lead to dental and skeletal fluorosis leading to many serious complications.
3. Certainly Lethal Dose (CLD) 32-64 mg of fluoride/ kg body weight.

        Safely Tolerated Dose (STD) 8-16 mg of fluoride / kg body weight.

4. Prior to the introduction of water fluoridation as a public health measure, the principal use of fluoride known to the layman was that of a pesticide. Most fatalities associated with fluoride toxicity have resulted from industrial accidents. The toxic effects of fluoride can be classified as acute, due to a single ingestion of a large amount of fluoride, or chronic, due to a long term, ingestion of smaller amounts.
5. Dental fluorosis > times optimal exposure to fluoride for until 5 years
Skeletal fluorosis: 10-25 mg / day for duration of 10-20 years.

The most frequently encountered adverse effects of topical fluoride therapy include nausea, vomiting, diarrhea, increased salivation, dehydration and thirst.

6. Excessive intake of fluoride during tooth development can use enamel fluorosis due to defective amelogenesis. Clinically it presents as a lusterless, opaque white patches in the enamel which may become mottled, striated or pitted. Mottled areas may become yellow or brown. Hypo plastic areas may also be present to such an extent in severe cases that normal tooth form is lost. Theses teeth however are resistant to carious attack.
7. Skeletal fluorosis was first reported by Vishwanathan in 1935 to be prevalent in residents of Madras presidency in 1933. However, Shortt, (1937) was the first to identify the disease as "fluorosis" in individuals in Nellore district of Andhra Pradesh. At water fluoride levels over 8 ppm, skeletal fluorosis may develop. Its symptoms are varied in nature, ranging from severe pain in the back bones, joints, hips, stiffness in joints and spine, outward bending of hands and legs called "knock knee syndrome", and in severe form patient may be completely immobilized causing "crippling fluorosis.
8. Excessive fluoride ingestion may also lead to cardiac problems and respiratory failure caused by blocking and calcification of blood vessels.
9. Pregnant lactating women form one of the most vulnerable groups. Excessive fluoride intake may cause damage to developing foetus.
10. A high fluoride strategy cannot be followed to avoid the potential for adverse effects (e.g., fluorosis) due to over exposure to fluoride.
11. Although fluoride presents no problem when used properly, among certain parts of the world, there has been the suggestion that fluoride exposure should be limited.

All these limitations and potential side effects have prompted researchers to look for non-fluoride alternatives for remineralisation of the dental tissue.

Conclusive concepts:
The awareness about oral health is increasing in present days. Most of the patients are now shifting from the curative to preventive health care. The oral care providers should change their treatment plan from curative to preventive aspects with the help of these simple remineralization tools, techniques and products. This will help in maintaining the hard tissue health throughout the patient's life. Therefore, preventive and therapeutic approach must consider the set of these factors. Cariogenic microorganisms colonize the tooth surface and form dental biofilm. Therefore, preventive and therapeutic approach must consider the set of these factors. Cariogenic microorganisms colonize the tooth surface and form dental biofilm. Reducing the levels of caries associated bacterial species in dental plaque is one of the preventive strategies to prevent the initiation of caries and to treat the disease. (Lynch, 1996 and Johanssonet et al., 2009).[56, 57] Furthermore, to prevent secondary caries that may be related to the presence of residual bacteria under restorations, Meja`re et al. (1979) [58] and Magni et al. (2008), [59] the use of an antibacterial treatment after caries removal seems to be meaningful (Polydorou et al., 2006). [60] To arrest caries progression, several antibacterial treatments have been proposed in order to mechanically and/or chemically reduce biofilm formation, Mu¨ller et al. (2007), [61] Banerjee et al. (2000), [62] Sbordone and Bortolaia, (2003) [63] and Baehni and Takeuchi, (2003), [64] and reduce the amount of residual bacteria after caries removal (Polydorou et al; 2006, Imazato et al., 1998, Ozer et al., 2005 and Wicht et al., 2004.[60, 65, 66, 67] Nowadays, to treat dental caries, pharmaceutical approaches have gained popularity.Such approaches give the opportunity of caries treatment without drilling.

Fluoride (F) has been a useful instrument and is one of the most effective remineralizing agents in caries prevention (Murray et al; 1991). [68] Over the last 25 years, the decline in dental caries experienced in most industrialized countries can be attributed largely to the widespread use of fluoride (Brambilla, 2001). [26] Nevertheless, some concern has been expressed that with the wide array of both rescription and over-the-counter fluoride products now being marketed in every country, the total fluoride intake has increased to perhaps harmful levels. Chronic low-level exposure to fluoride can present problems in organ systems (gastro-intestinal, genito-urinary and respiratory) of

normal individuals (Brambilla, 2001). [26] The prevalence of dental fluorosis, on the other hand, has increased noticeably in non-fluoridated areas and to a lesser extent in optimally fluoridated areas (Brambilla, 2001., Pendrys,1991 and Newbrun,1992).[26, 69, 70] Therefore, it is still necessary to seek alternative, effective non-fluoride agents that can provide a complete cure for caries. Fluoride has long been known to be effective in protecting the dental enamel from caries by reducing enamel dissolution and enhancing enamel remineralization processes, and is introduced into the oral environment via self (e.g., dentifrices, rinses) or professional applications (e.g., varnishes, foams, and gels fluoride-releasing restorative materials). During the process of demineralization of enamel, apatite is reduced to simpler compounds or ions and apatite can be reformed during the process of remineralization. Apatite is the most stable and least soluble form of calcium phosphate compounds and its formation during mineralization, is therefore, desirable. One of the most important actions of fluoride is its ability to increase the formation of apatite during remineralisation. Brown et al. (1977)[71] suggested that due to its ability to enhance remineralization of carious enamel, the outer layer of the apatite crystal may take up fluoride that gets incorporated into the new crystal structure in increased amounts to form fluorapatite. This remineralized enamel will thus be more resistant to future demineralization than the surrounding unaffected enamel. Several mechanisms have been proposed to achieve the anti-caries effects of fluoride, including the formation of fluorapatite, the enhancement of remineralization, interference with ionic bonding during pellicle and plaque formation and the inhibition of microbial growth and metabolism (Niessen et al., 1997). [72] Fluoride can be used along with other components such as sodium, zinc, tin, titanium. The newly introduced titanium fluoride (TiF) exhibits enhanced uptake of calcium and TiF pretreated enamel also shows decreased loss of calcium during demineralization (Exterkate and Ten, 2007). [73]

At present, it is known that the action of fluoride (F) in interfering in the process of caries lesion formation is not systemic, but local. For this purpose, fluoride must be present in the biofilm and saliva at the time in which the biofilm is exposed to sugar, or after its removal during tooth brushing (Cury and Tenuta, 2009). [74] It is noted that fluoride, even in low concentrations, interferes in the process of caries development. Hydroxyapatite (HA) dissolves at a pH of around 5.5, while fluorapatite (FA: crystallized form of F, Ca and P) dissolve at a pH close to 4.5. When the oral pH remains between 4.5 and 5.5, the process of HA demineralization occurs, in which there is release of Ca, P and hydroxyls in the oral environment. If there is fluoride present, these ions react with it and fluorapatite is formed which, saturated at this pH, is deposited on the tooth surface. This compensates the mineral loss occurring at pH between 4.5 and 5.53. However, this mineral reposition occurring by means of fluorapatite formation is not considered remineralization, but in fact, rather as an inhibition of demineralization, because the mineral component deposited differs from the one lost. Furthermore, fluorapatite is deposited on the tooth surface, while the Ha is dissolved in the subsuperficial region of the tooth (Cury and Tenuta, 2009). [74] As previously stated, caries is essentially a disease related to tooth demineralization. A considerable body of literature has established the use of fluoride as being an important agent in dental remineralization. The interaction between the ions of Ca and fluoride, which form fluorapatite, is greater between the ions of Ca and OH, which forms HA. This gives fluorapatite greater stability and lower solubility. Therefore, fluoride is the main component of dentifrices and mouth washes (Reynolds, 2008). [75] The indirect effect of fluoride on the reduction of dental demineralization, when pH falls, is complemented by the natural effect of fluoride on dental remineralization, when the pH rises, promoting the reposition of Ca and P ions present in biofilm fluid. If the demineralized surface is submitted to tooth brushing, the saliva is capable of promoting remineralization. However, if there is presence of fluoride, this process is potentiated (Cury and Tenuta, 2009). [74] Dentifrices and fluoridated oral solutions have been demonstrated to diminish the activity of caries in controlled randomized clinical trials. The efficacy of these products arises from their ability to incorporate fluoride ions in the plaque and tooth enamel (Pulido et al., 2008). [76] However, the toxicological potential of fluoridated compounds must be pointed out. There is risk of acute intoxication occurring when a large quantity of fluoride is ingested. There may also be chronic intoxication when there is consumption of a concentration of fluoride in excess of the adequate amount for a longer period of time.

Arnold, in 1957, was the first to mention the post-eruptive effect of fluoride in the drinking water and the ability of topical fluoride to reduce the incidence of caries (Mellberg et al., 1983). [77] Fluoride works primarily via topical mechanisms which include inhibition of demineralization at the crystal surfaces inside the tooth, enhancement of remineralization at the crystal surfaces and, at high concentrations, inhibition of bacterial enzymes. Low levels of fluoride in saliva and plaque help prevent and reverse caries by inhibiting demineralization and enhancing remineralization (Laurence, 2009). [78] The mechanism by which fluoride increases caries resistance may arise from both systemic and topical applications of fluoride and can be broadly grouped as follows:-increased enamel resistance, increased rate of maturation, remineralization of incipient caries, interference with microorganisms and improved tooth morphology (Shashi et al., 2013). [79] When a carious lesion is already present, an acidic challenge is

frequently occurring. Under this circumstance, when pH is below 5.5 – a critical pH for dental enamel, the remineralization can naturally take place since saliva is generally supersaturated with respect to dental enamel (Featherstone et al., 1999). [80] If fluoride is present in this acidic medium during dissolution of hydroxyapatite, the solution will be highly supersaturated with respect to hydroxyapatite and all potential mineral loss will actually be preserved in the partially demineralized dental crystals. In other words, traces of fluoride in the fluid phase can control mineral loss (Featherstone et al., 1999). [80] Thus, the frequent presence of fluoride in the oral environment during the acidic challenge is as relevant as it is its effect of incorporation. Hence the presence of fluoride at high concentrations is a key strategy for caries control or arresting carious lesions (Featherstone et al., 1999). [80]

Mineral or ionic technologies:
Fluoride works primarily via topical mechanisms which include inhibition of demineralization at the crystal surfaces inside the tooth, enhancement of remineralization at the crystal surfaces (giving an acid resistant surface to the reformed crystals), and, at high concentrations, inhibition of bacterial enzymes. Low levels of fluoride in saliva and plaque help prevent and reverse caries by inhibiting demineralization and enhancing remineralization. On the other hand, high levels of surface fluoride can increase resistance to carious lesion formation and to dental erosion. Numerous laboratory studies have shown that low levels of fluoride, typical of those found after many hours in resting plaque and saliva, and resulting from the regular use of fluoride dentifrices, can have a profound effect on enamel demineralization and remineralization. Fluoride present in the oral fluids alters the continuously occurring dissolution and reprecipitation processes at the tooth-oral fluid interface. Remineralization of incipient caries lesions is accelerated by trace amounts of fluoride. High concentration fluoride therapies lead to deposition of aggregates of calcium fluoride on the surface, which then acts as a reservoir of fluoride. The rate of fluoride release is enhanced at lower pH levels. A pH less than 5 causes loss of adsorbed phosphate, and triggers a slow dissolution of the calcium fluoride. To increase its surface area, nano-sized particles of calcium fluoride have been prepared, with a diameter of some 41nm.Such particles are many times larger than those in Recaldent™ (CPP-ACP or CPP-ACFP), where the nanoclusters are only 2 nm in diameter. In laboratory studies where there is no saliva or plaque present and prolonged contact with remineralizing agents is assured, artificial solutions containing calcium and phosphate, and fluoride (at levels of 1 ppm) can result in mineral gain in natural and laboratory-created white spot carious lesions over a 4 week period. A key salivary parameter to consider in terms of remineralization is the extent of variations in calcium concentration between resting saliva (where it is low) and stimulated saliva (where it is higher). While phosphate levels in resting saliva do not vary markedly, large fluctuations in calcium concentrations occur in the one individual. Differences in calcium concentration have important implications for the critical pH and for the possibility of remineralization, since the latter will not occur when the degree of saturation of saliva with respect to tooth mineral is low. In other words, remineralization may be enhanced by providing low levels of bio-available calcium and phosphate ions, in conjunction with minimal amounts of fluoride (<1 ppm). Conversely, under low calcium concentrations, remineralization is a chemical impossibility. There are significant inter-individual and time-related variations in pH, buffer capacity, and salivary concentrations of calcium and phosphate. These changes impact directly on the likelihood of mineral loss and gain, in terms of both dental erosion and dental caries. Saliva, enamel, bone, cementum, dentine and milk contain closely related phosphoproteins which bind and stabilize calcium and phosphate, orchestrating the behaviour of these ions in a pH dependant fashion. In fact, statherins in saliva, casein phosphoproteins in Recaldent products, and phosphoproteins in tooth structure share remarkable similarity. When hard tissues are demineralized, the phosphoproteins which remain influence the ability of this tissue to remineralize. The fluorides are still the keystone of non-invasive dental caries management, many of the alternative methods beyond fluoride have been developed and extensive research is still going on for the same (Bottenberg et al., 1998). [81] The increasing demand about the reminerilisation of dental caries through non invasive procedure beyond floride or with the use of another agent, which can work together with fluorides in achieving the desired goal of caries prevention. Achievements in the concept of bone repair and regeneration by bioactive materials were the inspiring base for gaining the same results to maintain the health of tooth enamel. These agents played significant role in the prevention of dental caries in modern dentistry and aimed at controlling the demineralization/remineralization cycle, depending on the microenvironment around the tooth.

Remineralization is the natural repair process for noncavitated 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. The composition and the concentration of inorganic ions in saliva and in dental plaque significantly influence the degree of saturation of the water-rich fluid which is in immediate contact with enamel. The critical role played by salivary components in controlling the equilibrium between de- and remineralization is ably demonstrated when salivary output is

compromised and patients suffer dramatic increases in risk for dental caries and/or dental erosion. Enhanced remineralization of white spot lesions by stimulated salivary flow (e.g. from chewing a sugar-free gum) illustrates dynamic protective effects of saliva. Protective properties of saliva which increase on stimulation include salivary clearance, buffering power, and degree of saturation with respect to tooth mineral. It has been noted in the dental literature that the design of experiments using dental caries or dental erosion models must take into account the static and dynamic effects of saliva. In the context of remineralization, an important component of saliva are its proteins, such as the glycoproteins which adsorb onto tooth structure to form the protective pellicle layer, and the phosphoproteins which regulate calcium saturation of the saliva. Pellicle is known to reduce mineral loss from enamel under conditions of acid challenge, more so for enamel than for dentine. Moreover, the early pellicle glycoproteins, acidic prolinerich proteins and statherin, are known to promote remineralization of the enamel by attracting calcium ions. Acidic proline-rich proteins bind strongly to hydroxyapatite, inhibit crystal growth of calcium phosphate salts from solutions supersaturated with respect to hydroxyapatite, bind calcium ions, and interact with several oral bacteria on adsorption to hydroxyapatite. Statherins, as well as histatins, and cystatins also exhibit affinities to mineral surfaces, and inhibit calcium phosphate precipitation. Some experimental systems such as in situ studies which use enamel slabs embedded into appliances allow full expression of the impacts of saliva, whilst some laboratory bench models exclude the involvement of saliva, and create nonsensical interpretations from the standpoint of clinical practice. Laboratory testing protocols using ionic solutions have significant limitations, most particularly related to their inability to simulate the complex biological processes involved. It appears that protective effects of salivary components and therapeutic agents act in a cooperative manner. An example would be the similar role played by salivary statherins and by the casein phosphopeptides in Recaldent™, both of which regulate the behaviour of calcium and phosphate, and stabilize calcium phosphate compounds. For Recaldent™ and other agents which interact extensively with saliva, it is essential that they are tested in models where human saliva is used, rather than with artificial saliva solutions which lack a complete repertoire of proteins, since studies which exclude salivary proteins will underestimate the true remineralizing actions of this agent. It is preferable that in situ models are used, with enamel or dentine slabs carried in the mouth and exposed to the normal oral environment. Such models explore the demin-remin balance in human subjects without actually causing caries in the natural dentition of those subjects.

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