Fluoride

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Abstract

It is known that fluoride helps to prevent tooth decay, however an excess of fluoride can cause enamel fluorosis. In this chapter, we will discuss current knowledge about fluoride and its effect on teeth, including dental fluorosis, fluoride and caries prevention, and enamel remineralizing agents.

15.1 Dental Fluorosis

Dental fluorosis is a developmental condition that affects the teeth. It is caused by overexposure to fluoride during the first 7–8 years of life, the period when most of the permanent teeth are being formed.

The potential for dental fluorosis increases with the level of systemic fluoride intake. Dental fluorosis resulting from high fluoride levels in underground water is an issue in specific regions of the world. Drinking water is usually the major source of the daily fluoride intake. However, in some parts of Africa, China, the Middle East, and Southern Asia (India, Sri Lanka), as well as some areas in the Americas and Japan, high amounts of fluoride are found in vegetables, fruit, tea, and other crops (WHO/UNICEF Joint Water Supply and Sanitation Monitoring Programme 2005). The atmosphere in these areas may have high levels of fluoride from dust in areas with fluoride-containing soils and gas, released from industries, underground coal fires, and volcanic activities (WHO/UNICEF Joint Water Supply and Sanitation Monitoring Programme 2005).

Teeth with mild dental fluorosis are more resistant to dental decay; however, severely fluorosed teeth are more susceptible to decay, most likely because of the uneven surface or loss of the outer protective layer (Ockerse and Wasserstein 1955). The primary pathological finding of fluorosed enamel is a subsurface porosity, along with hyper- and hypomineralized bands within the forming enamel (Fejerskov et al. 1974, 1975,

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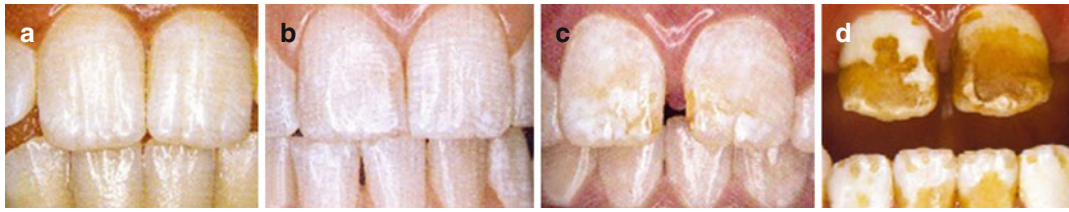

Fig. 15.1 Dental fluorosis. (**a**) Mild fluorosis with slight accentuation of the perikymata, (**b**) moderate fluorosis, showing a white opaque appearance, (**c**) moderate, white opaque enamel with some discoloration and pitting, (**d**) severe fluorosis [with permission from a reference (Denbesten and Li, 2011), Fig. 1] DENBESTEN, P. & LI, W. 2011. Chronic fluoride toxicity: dental fluorosis. Monogr Oral Sci, 22, 81–96

1977, 1979, 1991; Kidd et al. 1981; Kierdorf et al. 1993). Clinically, mild cases of dental fluorosis are characterized by a white opaque appearance of the enamel, caused by increased subsurface porosity. The earliest sign is a change in color, showing many thin white horizontal lines running across the surfaces of the teeth, with white opacities at the newly erupted incisal end. The white lines run along the "perikymata," a term referring to transverse ridges on the surface of the tooth, which correspond to the incremental lines in the enamel known as Striae of Retzius (Moller 1982; Kroncke 1966). At higher levels of fluoride exposure, the white lines in the enamel become more and more defined and thick. Some patchy cloudy areas and thick opaque bands also appear on the involved teeth. With increased dental fluorosis, the entire tooth can be chalky white and lose transparency (Moller 1982; Smith 1985). With higher fluoride doses or prolonged exposure, deeper layers of enamel are affected; the enamel becomes less well mineralized. Damage to the enamel surface, sometimes with subsequent staining of the porous enamel and exposed dentin, occurs in patients with moderate to severe degrees of enamel fluorosis (McKay 1952; Mottled Enamel. Am J Public Health Nations Health 1933) (Fig. 15.1).

15.1.1 Mechanisms of Enamel Fluorosis

Studies to determine the mechanisms by which fluoride results in dental fluorosis have used animal models. The most frequently used model to study fluorosis mechanisms is the rodent incisor, as it is not possible to do similar studies using human teeth. Fluoride can be given in drinking water beginning at 21 days, when rodents are weaned. At this time, the incisors are fully erupted; however, because the rodent incisor is a continuously erupting tooth, all stages of enamel formation are present, so that the effect of fluoride at each stage of enamel formation can be investigated.

Models to Study the Fluorosis Mechanisms Should Be Based on Comparable Concentrations to Those Found in Human Serum A difference between rodents and humans, which sometimes results in confusion as to the relevance of studies of fluoride mechanisms, is the fact that rodents must consume approximately 10 times the amount of fluoride in drinking water than humans to result in the same serum fluoride level and degree of fluorosis. For example, humans drinking 3–5 ppm fluoride in water (1 ppm F = 52.6 μM) have serum fluoride levels of 3–5 μM (Guy et al. 1976) which form fluorosed enamel. For a mouse to have similar serum fluoride levels, the mouse must ingest drinking water containing approximately 50 ppm F (Zhang et al. 2014). It is not known why rodents require 10 times the concentration of fluoride in their drinking water to have serum fluoride levels similar to humans. However, the fact remains that comparable serum fluoride levels should be used to assess the biological relevance of an animal model. Much confusion has resulted in interpretation of studies on fluorosis mechanisms because of these concentration differences in

fluoride ingested in water by rodents as compared to humans. Because of this, the relevance of rodent studies to fluorosis mechanisms in humans has been questioned and their relevance not clearly understood.

Similar issues relating to the relevance of the fluoride concentration used occur in vitro of fluoride mechanisms. Many in vitro studies expose cells to fluoride levels found in drinking water, which are in fact 50 times higher than would be found in serum. For example, 1 ppm F, which is equivalent to 52.6 μM F, ingested by humans in drinking water, results in serum fluoride levels of approximately 1 μM serum F. This suggests that the use of 1 ppm fluoride cell culture in vitro would actually represent fluoride levels approximately 50 times that likely are to be found at the cellular level in vivo, and the results obtained are not likely to be relevant to in vivo fluoride exposure to humans. Therefore, to understand the mechanisms by which fluoride may affect both enamel formation and other cells and tissues, experiments conducted and the interpretation of their results must be done with an understanding of biological relevance.

Fluoride Exposure Causes Both Hyper- and Hypomineralization of the Enamel Matrix Fluoride is a highly electronegative anion and, as such, enhances mineral formation. This local hypermineralization in the enamel matrix depletes the local reservoir or free calcium ions and then may also act as a physical barrier, impairing diffusion of ions and peptides, to result in a subsequent band of hypomineralized enamel (Guo et al. 2015). Therefore, within the matrix, it is possible that a more rapid mineral precipitation in the presence of fluoride may result in the presence of hypermineralized bands followed by hypomineralized bands in the enamel matrix (Bronckers et al. 2009).

Fluoride Exposure May Increase Acidification of the Developing Enamel Matrix Formation of hydroxyapatite biominerals (HAP) results in the formation of protons ($10Ca^{2+} + 6 HPO_4^{2-} + 2H_2O \rightarrow Ca_{10} (PO_4)_6 (OH)_2 + 8H^+$), which acidify the enamel matrix. Therefore, regulation of matrix pH by ameloblasts is crucial for sustained crystal growth. In the presence of fluoride, increased mineral formation may result in local acidification, which is buffered by amelogenin proteins in the enamel matrix at the secretory stage (Guo et al. 2015).

At the maturation stage, where the most of the enamel HAP mineralization occurs, the pH in the enamel matrix changes periodically between acidic (pH 5.8) and neutral (pH 7.2) (Sasaki et al. 1991; Smith 1998). Protons generated during HAP formation in the maturation stage are neutralized by bicarbonate secreted from the apical end of ruffled-ended maturation ameloblasts through anion exchangers of the Slc26a family (Jalali et al. 2014). Transmembrane proteins, including cystic fibrosis transmembrane conductance regulator, anion exchanger-2, carbonic anhydrase-2, and sodium hydrogen exchanger-1, are involved in this pH regulation mechanism (Guo et al. 2015; Lyaruu et al. 2008; Alper 2009; Concepcion et al. 2013). In the fluorosed enamel matrix, retention of amelogenin protein may also buffer pH changes in the matrix, secondary to mineral formation, thereby reducing the acidification of the matrix under ruffle-ended ameloblasts (Guo et al. 2015).

Bicarbonate is exchanged for chloride (Cl-) in the matrix, and with increased secretion of bicarbonate, the amount of chloride in the mineralizing enamel matrix is decreased. The reduced amount of Cl found in the fluorosed enamel matrix supports the hypothesis that increased enamel matrix acidification and subsequent neutralization occurs in the presence of increasing amounts of fluoride (Bronckers et al. 2015). Recent evidence has shown that maturation stage ameloblast modulation depends on Cl- (Bronckers et al. 2015), and therefore reduced Cl in the enamel matrix may be responsible for the fewer number of ameloblast modulations from ruffle-ended to smooth-ended ameloblasts, found in the presence of fluoride.

Amelogenins Are Retained in Fluorosed Maturation Stage Enamel Fluorosed maturation

stage enamel is characterized by a delay in the removal of amelogenin matrix proteins (DenBesten and Crenshaw 1984; Wright et al. 1996). It is possible that this delay in removal of amelogenins is due to altered ameloblast modulation (DenBesten et al. 1985; Smith et al. 1993). Other factors that may contribute to the retention of amelogenins in fluorosed enamel include increased binding of amelogenins to the fluoride-containing HAP crystals (Tanimoto et al. 2008), which may delay the removal of amelogenins from the enamel matrix. Recent studies in mice have also shown a reduced expression of KLK4, the proteinase responsible for hydrolyzing amelogenins and other matrix proteins in the maturation stage (Suzuki et al. 2014). A reduction in KLK4 could also delay the hydrolysis of amelogenins and their removal from the enamel matrix, resulting in less final mineral formation and a more hypomineralized enamel matrix. These effects of fluoride at the maturation are consistent with the observation that fluoride-induced subsurface hypomineralization can independently occur in the maturation stage, even without prior exposure to secretory stage enamel. However, fluorosis is most severe with fluoride exposure to all stages of enamel formation (DenBesten et al. 1985; Richards et al. 1985; Suckling et al. 1988).

Fluoride Can Alter Cell Function Amelogenesis is a dynamic interaction between the differentiating ameloblasts and the self-assembling mineralized matrix. The primary mechanisms responsible for the formation of fluorosed enamel appear to be related to effects on matrix mineralization. However, it is possible that fluoride may, to a lesser extent, directly affect cell function, though it is difficult to differentiate direct cellular effects from those caused by changes in the mineralizing matrix. Some studies have found that fluoride appears to alter the timing of gene expression in ameloblasts overlying fluorosed as compared to control enamel, possibly related to a fluoride-related enhancement of Gαq activity in secretory ameloblasts (Zhang et al. 2014).

15.1.2 Fluoride Effects on Dentin Formation

The dentin matrix is far less mineralized than the enamel matrix and is comparatively unaffected by fluoride. However, in vitro studies of mildly and moderately fluorosed human dentin, showing increased caries susceptibility (Waidyasekera et al. 2007), suggest that fluoride also alters dentin biomineralization. In support of this possibility, reduced dentin microhardness and increased dentin fluoride were shown to correlate enamel fluorosis severity (Vieira et al. 2005). Fluorosed dentin has been characterized as having increasingly disorganized dentin crystals (Kierdorf et al. 1993; Vieira et al. 2004, 2005; Nelson et al. 1989; Yaeger 1966; Waidyasekera et al. 2010), and structurally, severely fluorosed human dentin is described as the distinct layering of hypomineralized lines and extensive areas of interglobular dentin (Fejerskov et al. 1977), with the irregular and densely arranged dentinal tubules (Rojas-Sanchez et al. 2007). These studies indicate that fluoride-related changes can occur while primary dentin is formed.

15.2 Fluoride in Food and Water

Water Fluoridation One of the first attempts to provide effective caries control on a population basis was through the use of artificial water fluoridation programs. By the 1940s, there was a substantial body of literature comparing the prevalence and severity of dental caries among populations living in communities with differing levels of fluoride in the water. These studies showed that dental caries levels dropped sharply as water fluoride levels rose to 1.0 ppm. This was also the concentration at which prevalence of dental fluorosis began to increase in these same populations (Dean 1938). As a result of this work, 1 ppm F was determined to be the point at which one could expect to receive an optimal benefit with minimal side effects of dental fluorosis.

On January 25, 1945, Grand Rapids, Michigan, USA, became the first city in the world to adjust its water fluoride concentration to a level expected to reduce dental caries, and 10 years later, the study found that though mild forms of dental fluorosis were increased, dental caries was significantly decreased (Arnold et al. 1956). Other studies have continued to confirm the benefits of water fluoridation, though more recently the overall rates of caries were found to be dropping in the population at large (Brunelle and Carlos 1990). Caries rates throughout the world have followed similar trends, and interestingly, caries rates have decreased whether or not the local water supplies are fluoridated, most likely related primarily to the widespread worldwide expansion of the use of fluoride toothpaste after 1970. Recently, a Cochrane systematic review that evaluated the effectiveness of water fluoridation for the prevention of caries suggested the need to evaluate all sources of fluoride before such systems should be considered. The review concluded, "The decision to implement a water fluoridation programme relies upon an understanding of the population's oral health behavior (e.g., use of fluoride toothpaste), the availability and uptake of other caries prevention strategies, their diet and consumption of tap water and the movement/migration of the population." However, there was a significant association between dental fluorosis and level of exposure to fluoride (Iheozor-Ejiofor et al. 2015). In spite of the issues raised regarding fluoride, the use of fluoridated water has provided significant anticaries benefits. The American Dental Association, the US Center for Disease Control, and the World Health Organization all support water fluoridation. According to the (http://www.who.int/water_sanitation_health/oralhealth/en/index2.html), "Fluoridation of water supplies, where possible, is the most effective public health measure for the prevention of dental decay."

Salt Fluoridation A key objection to community water fluoridation is that it fails to provide consumers with a choice, as the only alternative is for consumers to purchase bottled water that is not fluoridated. One alternative to water fluoridation is salt fluoridation. To some, the use of salt fluoridation over water fluoridation is an attractive option. Fluoridated salt is generally sold side by side on grocery shelves with non-fluoridated salt; the choice is up to the individual consumer as to which one they prefer.

Originally introduced in 1955 in Switzerland as an extension of programs that utilized iodized salt for the prevention of thyroid conditions (Burgi and Zimmermann 2005), the fluoridation of table salt has been demonstrated to provide caries reductions on par with water fluoridation programs (Marthaler 2005) when the majority of the salt consumed is fluoridated. Fluoride concentrations in salt ranging from 90 mg/kg up to 350 mg/kg have been tested, with some studies suggesting the level of 250–300 mg/kg as being optimal. One study demonstrated that salivary fluoride levels after eating a meal prepared with salt fluoridated at 250 mg/kg were similar to those of individuals exposed to water fluoride levels of 1 mg/l (Hedman et al. 2006). A level of 200 mg/kg is considered the minimum level necessary to provide a reasonable caries benefit (Sampaio and Levy 2011), suggesting that salt fluoridation can result in increased salivary fluoride.

Human studies that assessed the effectiveness of salt fluoridation in Columbia, Hungary, and Switzerland confirmed the effectiveness of this approach, demonstrating results that were not unlike those seen with early water fluoridation programs (Marthaler and Petersen 2005; Jones et al. 2005). Fluoridated salt is relatively easy to deliver to consumers through a range of channels, including the use of domestic salt, participation in school meal programs, and bread made in local bakeries. One of the advantages to the use of salt fluoridation is its availability in areas where fluoridated toothpastes are not broadly available or are considered to be too expensive. However, when combined with the use of fluoridated toothpastes, fluoride exposures may reach above optimal levels (Baez et al. 2010).

One example that highlights the effectiveness of fluoridated salt comes from Jamaica, where virtually all salt intended for human consumption has been fluoridated since 1987 (Jones et al. 2005). Although fluoride toothpastes have been available there since 1972, an oral health survey conducted in 1984 showed extremely high caries rates in Jamaican children, with the assumption being that toothpastes were generally not used on a regular basis (Table 15.1). In 1986, the Jamaica Parliament approved a salt fluoridation program, as water fluoridation was deemed to be technically unfeasible in the region. The natural concentration of fluoride in the water was less than 0.3 mg/ml. At the time, Jamaica had only one supplier of salt, which made salt fluoridation a viable option. Salt was fluoridated at 250 mg/kg, using potassium fluoride, with technical guidance provided by the Pan American Health Organization (PAHO). Urinary excretion studies, which are commonly used to monitor excessive ingestion of fluoride (Marthaler and Schulte 2005) conducted at baseline and after 20 months of Jamaica's salt fluoridation program indicated fluoride concentrations were no greater than those that would be expected for a temperate climate where water fluoridation programs were in place. A follow-up survey in 1995 confirmed the effectiveness of the program, with dramatic reductions in caries noted in each of the age groups measured (Table 15.1).

Salt fluoridation is broadly available in many Latin American countries, with the exception of Brazil, Chile, and Panama, where fluoride toothpastes are commonly used. One issue regarding the exclusive use of fluoridated salt is the potential for erratic exposure; usage can vary significantly from one individual to another. Another issue is the lack of standardized processes for fluoridated salt in countries where there are multiple producers of salt, with no effective surveillance mechanisms in place. From an economic viewpoint, salt fluoridation appears to be a cost-effective measure, with one report indicating the per capita costs average between 0.015 and 0.030 (USD) per year (Gillespie and Marthaler 2005). However, recent reviews point to the lack of available, randomized clinical trials comparing salt fluoridation to other methods of caries prevention (Espelid 2009; Cagetti et al. 2013).

Table 15.1 Mean number of decayed, missing, or filled permanent teeth (DMFT) in Jamaican children, 1984 and 1995

Age (years)	Mean number of DMFT		Percent decrease in DMFT
	1984	1995	
6	1.71	0.22	87 %
12	6.72	1.08	84 %
15	9.60	3.02	68 %

Adapted from: Jones et al. (2005)

Milk Fluoridation In addition to salt and water fluoridation programs, milk fluoridation is another approach that is used in some geographic areas. Like water fluoridation, this approach does not require a change in consumer behaviors in order to provide an anticaries benefit. The basic premise is that ingestion of fluoridated milk will maintain salivary fluoride levels at levels similar to those achieved in individuals living in areas of optimally fluoridated water systems.

While individual trials have suggested significant benefits associated with milk fluoridation programs (Rusoff et al. 1962; Stephen et al. 1984), systematic reviews of fluoridated milk have concluded that there is a lack of well-controlled randomized clinical trials to confirm the effectiveness of this approach (Espelid 2009; Cagetti et al. 2013; Yeung et al. 2005, 2015). Though some effectiveness has been shown for primary teeth (Cagetti et al. 2013), as noted in a recent Cochrane review: "There is low quality evidence to suggest fluoridated milk may be beneficial to schoolchildren, contributing to a substantial reduction in dental caries in primary teeth. Additional randomized clinical trials of high quality are needed before we can draw definitive conclusions about the benefits of milk fluoridation"(Yeung et al. 2015).

15.3 Fluoride and Remineralizing Agents

Fluoride in the Biofilm Dental caries occurs when bacteria in a biofilm produce lactic acid by saccharolytic fermentation. This acid can penetrate through to the tooth surface that is protected by pellicle, a natural protective protein barrier, and dissolve the hydroxyapatite crystals in subsurface enamel, resulting in the formation of subsurface lesions (Levine 2011; Amaechi and van Loveren 2013; Buzalaf et al. 2011). If fluoride is present in the plaque fluid when bacteria produce acids, it will penetrate along with the acids through the plaque subsurface and adsorb to apatite crystal surfaces. When the pH returns to pH 5.5 or above, the saliva, which is supersaturated with calcium and phosphate, provides calcium and phosphate to bind to the fluoride ions and form fluorapatite mineral, which is relatively less acid soluble than the carbonated hydroxyapatite mineral of a natural tooth (Amaechi and van Loveren 2013; Buzalaf et al. 2011; Stoodley et al. 2008).

Fluoride, which is a single, highly electronegative ion, operates via two primary mechanisms: inhibiting enamel demineralization and enhancing the natural process of enamel remineralization (ten Cate and Featherstone 1991). In addition, fluoride can be incorporated into bacterial biofilms and, if present at high enough concentrations, can inhibit enolase (Qin et al. 2006). Enolase catalyzes the production of phosphoenolpyruvate, a precursor of lactic acid from 2-phosphoglycerate, during glycolysis. Oral bacteria utilize the phosphoenolpyruvate transport system to transfer mono- and disaccharides into the cytosol. Fluoride not only inhibits lactic acid production but also the phosphoenolpyruvate transport system-mediated uptake of saccharide substrates.

Of importance to both of the primary mechanisms of action for fluoride is the transport of fluoride through the biofilm to the enamel surface. Studies of the transport of fluoride through the biofilm are conflicting. One group of researchers showed that exposure of enamel to NaF (1000 ppm F-) for 30 or 120 s (equivalent to toothbrushing) or for 30 min, resulted in increased plaque fluoride concentrations near the saliva interface, while concentrations near the enamel surface remained low. Fluoride penetration increased with duration of NaF exposure, and removal of exogenous fluoride resulted in fluoride loss and redistribution. The authors concluded that penetration of fluoride into plaque biofilms during brief topical exposure is restricted, which may limit anticaries efficacy (Watson et al. 2005). However, another study showed that following the use of a 0.2% fluoride rinse, fluoride penetrated through the biofilm, causing some effect on the viability of the biofilm mass (Rabe et al. 2015). Although there are questions that still need to be answered with respect to how fluoride impacts the biofilm, it is clear that both the application and the retention of fluoride in plaque, plaque fluids, and oral tissue reservoirs play important roles in overall effectiveness of fluoride (Zero 2006).

15.3.1 Fluoride Delivered from Oral Care Products

Fluoride is widely used by oral healthcare providers to help prevent dental caries. Fluoride is available in different preparations ranging from low (0.25–1 mg per tablet; 1000–1500 mg fluorine per kg in toothpaste) to high concentrations (liquids containing 10,000 mg/L, gels containing 4000–6000 mg/kg), and varnishes (most of which contain 22,600 mg/kg) may be used for local topical applications (Slooff et al. 1988). In the USA, where fluoride products are regulated by the US Food and Drug Administration as drugs, only three sources of fluoride are allowed for inclusion in oral care products, as defined by the US caries monograph (Federal Register 1995). These include stannous fluoride (SnF_2), sodium fluoride (NaF), and sodium monofluorophosphate (Na_2FPO_3). In the European Union, where

fluoride products are regulated as cosmetics, a much broader range of fluoride sources and combinations are allowed (Lippert 2013), though some of these have never been proven effective in well-controlled caries clinical trials.

The anticaries efficacy of fluoride is dependent not only on the fluoride compound used but also on the concentration and contact time of fluoride on oral surfaces, the method of delivery of the agent itself, and the bioavailability of fluoride in the mouth after use. Simply delivering fluoride from an oral care product is not as important as the ability of the agent to react with exposed tooth surfaces and to be retained in oral fluids post application (Zero 2006). The anticaries benefits of fluoride toothpaste have been confirmed in numerous well-controlled clinical trials. Clinically effective fluoride toothpaste formulations, which are used all over the world as a primary means of delivering effective caries control, have been credited with the dramatic decline in caries in multiple geographies (Zero 2006). Multiple reviews have confirmed that other approaches to deliver fluoride, such as rinses, gels, and varnishes, are also effective at providing caries control. The effectiveness of fluoride products may be affected by individual susceptibility to caries, fluoride source and level, frequency of use, and overall oral hygiene. In addition, some improvement in caries protection may be provided through the combined use of fluoride toothpastes with another topical fluoride therapy, particularly for high-risk patients (Marinho 2009).

15.3.2 Other Remineralizing Agents

Calcium and phosphate from saliva provide a natural means for remineralization processes to occur. After a cariogenic acid challenge, salivary flow results in buffering to a more neutral pH, which encourages the natural replacement of lost minerals back into the tooth surfaces. In some instances, and with extended duration of challenges, the natural remineralization processes are insufficient to maintain an effective level of mineral balance. Fluoride aids in this process by enhancing the deposition of both calcium and phosphate, along with the fluoride, into demineralized regions of the tooth surface (ten Cate and Featherstone 1991; ten Cate 1999).

Newer remineralization therapies are intended to enhance the natural remineralization process by providing elevated levels of calcium and phosphate to supplement the levels provided by saliva (Pfarrer and Karlinsey 2009; Cochrane et al. 2010). The goal of these therapies is to increase subsurface diffusion of calcium and phosphate into the tooth surface, without increasing calculus formation, and to have remineralization effects at least equivalent to those of fluoride. Various approaches have been suggested, including combining remineralization agents with fluoride to enhance the efficacy of fluoride, using remineralization agent in combination with lower levels of fluoride to decrease the potential for dental fluorosis in younger children, and using remineralization agents alone, with only background exposure to fluoride (Zero 2006). Vehicles proposed for the delivery of remineralization agents have included not only toothpastes but also mouth rinses, gels, lozenges, chewing gums, and various foods and beverages. A number of remineralization therapies have been incorporated into commercial products and are currently being sold in the market. These include Recaldent™ (CPP-ACP – GC Corporation, Alsip, IL., USA), NovaMin® (GlaxoSmithKline, Brentford, UK), and Tricalcium Phosphate (TCP – 3M ESPE, St Paul, MN, USA). All of these approaches are based on the delivery of calcium and phosphate to the tooth surface.

Recaldent™ combines casein phosphopeptide (CPP) from milk with amorphous calcium phosphate (ACP), to stabilize ACP in the dental plaque biofilm. CPP-ACP is claimed to provide a reservoir of calcium and phosphate ions to maintain a state of supersaturation with respect to tooth enamel, to buffer plaque pH, and to provide ions necessary for remineralization of subsurface lesions.

NovaMin® is an inorganic amorphous calcium sodium phosphosilicate (CSPS), belonging

to a class of materials which are known as "bioactive glasses." In the presence of water or saliva, NovaMin® releases sodium ions, which is intended to increase the local pH and initiate the release of calcium and phosphate. The calcium-phosphate complexes crystallize into a carbonated hydroxyapatite, which is chemically and structurally similar to biological apatite.

Tricalcium phosphate (TCP) is a bioactive formulation of β-tricalcium phosphate that is claimed to work synergistically with fluoride to enhance mineralization of subsurface lesions when compared to using fluoride alone. When used in toothpaste formulations, a protective barrier is created around the calcium, allowing it to coexist with the fluoride ions. During toothbrushing, TCP comes into contact with saliva, causing the barrier to dissolve and release calcium and phosphate.

Another approach, CaviStat™, was a technology that combined calcium carbonate with arginine bicarbonate. A published clinical study compared the effectiveness of a dentifrice formulated with these ingredients, showing the product was more effective than the fluoride control (Acevedo et al. 2005). However, the study was poorly controlled, with the test product being used under supervised conditions and the F-control product being used under ad-lib conditions, and had not been repeated. The technology has recently been marketed under the trade name Pro-Argin™ and is currently sold outside the USA in combination with fluoride.

In addition to direct remineralization therapies, agents such as xylitol are reported to work indirectly to promote remineralization by decreasing bacteria and bacterial function. This approach is intended to create an environment where reparative remineralization is optimized. Xylitol is a 5-carbon sugar alcohol that is commonly found in birch tree sap and naturally occurring in some fruits and vegetables. Like all of the sugar alcohols, it is noncariogenic. However, much research has focused on whether or not it is also anticariogenic. It is believed that xylitol works to prevent cavities in multiple ways. Bacteria cannot break down xylitol into acid as they do from other fermentable sugars (i.e., sucrose, glucose, fructose, dextrose, etc.). When bacteria ingest xylitol, they do not consume as much of other fermentable sugars, which reduces acid production. Xylitol can help control the number of acid-producing bacteria in the mouth, which can in turn help prevent cavities. It is available in many commercial product forms, such as gums, mints, toothpastes, and mouth rinses. Xylitol is usually measured in grams, and studies show the recommended therapeutic dose is 6–11 g per day. Ingestion of more than 25–30 g in one day may result in an upset stomach and/or diarrhea. Xylitol can be very harmful, even potentially fatal, to dogs, as they cannot metabolize it like people can.

Unfortunately, in order for xylitol to be effective, it is necessary to essentially remove all other sources of fermentable sugar that the oral bacteria are likely to ingest. The most successful product studies using xylitol have come from chewing gum studies, and in those study subjects had to use 5–6 sticks per day in order to demonstrate effectiveness (Marinho 2009). Other studies were those such as the Turku sugar studies, in which xylitol was shown to be effective; however, the trial involved essentially complete substitution of sucrose with xylitol over the course of the 2-year clinical study (Scheinin et al. 1976). A recent Cochrane review (Riley et al. 2015) concluded that fluoride toothpaste containing xylitol may provide a slight improvement in anticaries benefits compared to fluoride alone; however, there is little evidence to support a significant anticaries benefit for products formulated only with xylitol.

In theory, the use of remineralization therapies makes technical sense, and both in vitro and in situ studies have suggested these approaches may provide enhanced mineralization benefits (Pfarrer and Karlinsey 2009; Reynolds 2009; Karlinsey et al. 2010). However, at present, there is little clinical evidence available to confirm that these approaches provide any greater benefit than fluoride, working in combination with natural levels of calcium and phosphate in saliva. For now, fluoride remains the most well-established remineralization therapy available.

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