Current Concept on the Anticaries Fluoride Mechanism of the Action

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ABSTRACT

The paper discusses a possible new concept of the role of fluoride and its mechanism of action in caries prevention. In the past fluoride inhibition of caries was ascribed to reduced solubility due to incorporation of fluoride (F⁻) into the enamel minerals (firmly bound fluoride or fluorapatite). Based on the new findings, it appears that fluoride, either released into or present in the fluid phase bathing the hard tissue, is more important for the reduction of caries development and progression. There is convincing evidence that fluoride has a major effect on demineralization and remineralization of dental hard tissue and that it interferes with acid production from cariogenic bacteria. The provision of dissolved fluoride is the key to successful therapy. The source of this fluoride could either be fluorapatite or calcium fluoride (CaF₂) (like) precipitates, which are formed on the enamel and in the plaque after application of topical fluoride. The precipitates of calcium fluoride do not dissolve quickly as was initially believed. Calcium fluoride coating at neutral pH by pellicle proteins and phosphate is the main reason for this. The dissolution of the fluoride from calcium fluoride is pH dependent. At lower pH, the coating is lost and an increased dissolution rate of calcium fluoride occurs. The CaF₂, therefore, act as an efficient source of free fluoride ions during the cariogenic challenge. These are subsequently incorporated into the enamel as hydroxyfluorapatite or fluorapatite.

Introduction

The mechanism of the cariostatic effect of fluoride (F⁻) is still not clearly understood. In the past caries inhibition with fluorides was ascribed to the reduced solubility of the enamel due to incorporation of F⁻ into the enamel minerals during tooth formation¹. However, recent studies have shown that the presence of fluoride in the enamel, even at very high levels, is not directly responsible for the caries preventive effect of fluoride. Recently, it was found that even shark enamel containing nearly pure fluorapatite had a limited resistance to caries attack in an oral human caries model². Consequently, fluoridation of the enamel and production of high levels of incorporated fluoride would not be sufficient to inhibit tooth decay. Some investigators have shown that fluoride in the so-

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lution surrounding the apatite crystals inhibits demineralization much more effectively than fluoride incorporated in the crystals\(^3\)\(^5\).

There is now much evidence which indicates that the caries preventive action of fluoride is primarily post eruptive through the »topical« effect, which includes:

- inhibition of demineralization
- enhancement of remineralization
- inhibition of bacterial activity in the plaque

Research indicates that topicals which are used frequently, such as daily use of dentifrices and mouthrinses can enhance remineralization and retard demineralization of enamel. The marked caries reduction in many countries over the last three decades is thought to be mainly the result of the widespread and frequent use of low concentrations of fluorides mainly via toothpastes\(^6\)\(^7\).

There is evidence that a major part of the fluoride which is retained on the teeth during topical application is calcium fluoride (CaF\(_2\)) or calcium fluoride-like material. Calcium fluoride is the most likely source of free ions during cariogenic challenges, which are subsequently incorporated into enamel as hydroxyfluorapatite or fluorapatite\(^8\). Thus, in the last few years understanding of the cariostatic mechanism of fluorides has changed fundamentally.

The aim of the present paper is to describe the current concept on the mechanism of the fluoride cariostatic effect and propose recommendations for future use of fluoride.

### The Chemical Properties of Enamel

Highly calcified enamel has approximately 96% mineral by weight, 1% organic matter and 3% water\(^9\). The solid phase of enamel consists mainly of crystallized calcium phosphate, that persist in different forms. X-ray diffraction analyses have shown that enamel minerals come mainly as hydroxyapatite and some less stable forms such as dicalciumphosphathydrat (DCPD), brushit or octacalciumphosphat (OCP). The mineral component of human dental enamel is basically an impure calcium hydroxyapatite. Carbonate is the most abundant impurity. Carbonated calcium hydroxyapatite is more soluble than calcium hydroxyapatite, especially in acidic media\(^10\)\(^-\)\(^12\). The pure hydroxyapatite Ca\(_{10}\)(PO\(_4\))\(_6\)(OH)\(_2\) allows the incorporation of many ions that fit in the crystallite structure and affect its solubility. The substitution in the hydroxyapatite crystal occurs during development with carbonate, magnesium, fluoride, etc. Fluoride improves the quality of mineralized tooth tissues in general by reducing the relative amounts of carbonated apatite. The reaction between hydroxyapatite and low concentrations of fluoride has been postulated to be an ionic exchange in which fluoride replaces and assumes the positions of the hydroxyl ions in the crystal lattice structure. The replacement of hydroxyl groups with the smaller fluoride ions should result in a more stable apatitic structure. If the OH\(^-\) ion in pure hydroxyapatite is completely replaced by a fluoride ion (F\(^-\)) the resulting mineral is fluorapatite Ca\(_{10}\)(PO\(_4\))\(_6\)F\(_2\)\(^9\). However, even in severely fluorosed human enamel such complete substitution is never achieved. The pure fluorapatite practically can never be found\(^13\). Only 10% of the hydroxyl groups can be substituted by fluoride in the surface enamel. The compound hydroxyapatite-fluorapatite is formed when the hydroxyl positions are only partially replaced by fluoride ion.

### Dental Caries

Dental caries is localized, progressive destruction of the tooth initiated by acid dissolution of the outer tooth surface. In the presence of the fermentable carbohy-
drate, organic acids are produced by plaque microorganisms which colonize the tooth surface. Some of the dental plaque bacteria, such as Streptococcus mutans and Lactobacillus are acidogenic. The acids (i.e. lactic, pyruvic, acetic, propionic, butyric) can dissolve the calcium phosphate mineral of the enamel or dentine (demineralization)\textsuperscript{14,15}. The acids diffuse through the plaque into the pores of the sound enamel surface, releasing hydrogen ions, which can dissolve the underlying enamel. The dissolved mineral ions, calcium and phosphate will then back-diffuse into the surface layer and induce the precipitation of the mineral phases in this region. At the same time, some of the dissolved mineral ions will diffuse out of the enamel surface to the oral environment. It is known that incipient or small carious lesions (»white spot lesion«) in human enamel consist of a subsurface area of demineralization with an overlying, apparently intact, surface zone. It is considered that the enamel surface layer is a result of reprecipitation of minerals (remineralization) dissolved from the subsurface\textsuperscript{16}. The leaching calcium and phosphate from enamel can cause collapse of the tooth structure and formation of a cavity. Demineralization and remineralization can be considered a dynamic process, characterized by the flow of calcium and phosphate out of and back into the enamel.

The saliva plays an important role, including buffering (neutralizing) the acid and providing minerals that replace those dissolved from the tooth during demineralization challenge. The enamel surface is in constant contact with saliva which is considered to be saturated with certain calcium phosphate salts, thereby maintaining the integrity of the enamel surface. It was found that within physiological pH limits the salivary content of calcium and inorganic phosphate was sufficient to supersaturate the saliva with respect to hydroxyapatite. The protective factors, which include salivary calcium, phosphate and proteins, salivary flow, and fluoride in saliva can balance, prevent or reverse dental caries\textsuperscript{14}.

The Role of Fluoride in Caries Prevention

There are three principle forms of fluoride ion reactivity with apatite: 1) Iso-ionic exchange of F\textsuperscript{–} for OH\textsuperscript{–} in apatite:

\[
Ca_{10}(PO_4)_{6}OH_2 + 2F^- \rightarrow Ca_{10}(PO_4)_{6}F_2 + 2OH^- 
\]

2) Crystal growth of fluorapatite from supersaturated solutions:

\[
10Ca^{2+} + 6PO_4^{3-} + 2F^- \rightarrow Ca_{10}(PO_4)_{6}F_2 
\]

3) Apatite dissolution with CaF\textsubscript{2} formation:

\[
Ca_{10}(PO_4)_{6}OH_2 + 20F^- \rightarrow 10CaF_2 + 6PO_4^{3-} + 2OH^- 
\]

The first two reactions may occur during long-term exposure to low fluoride levels in the solution (such as between 0.52 \(\mu\)mol and 0.52 mmol F/L (0.01 and 10 ppm F) from either systemic or latent topical sources. These reactions result in fluoride incorporation that, in a traditional sense, would be defined as »firmly« bound fluoride, since it is part of the apatitic structure. With the increasing fluoride concentration an additional chemical reaction with the formation significant calcium fluoride amounts begins to dominate. Fluoride concentrations ranging from 5.3 to 530 mmol/L (100–10,000 ppm F) are required to produce CaF\textsubscript{2} as a reaction product. These concentrations are present in topicals, such as professional gels and varnishes or over the counter toothpastes and mouthrinses\textsuperscript{17}. The name »loosely« bound fluoride has served as an alternative description for calcium fluoride formation.
Firmly-bound fluoride

It has been suggested that firmly bound fluoride is most beneficial for anticaries efficacy due to its lower solubility. Numerous studies have investigated the effects of fluoride on tooth mineral solubility. In all studies, fluorapatite was found to dissolve appreciably more slowly than hydroxyapatite. Moreno et al. has calculated the solubility product constants for various degrees of substitution of fluoride for hydroxyl in hydroxyapatite. The results showed that there was a steady decrease in the solubility of fluoridated hydroxyapatites, with increasing values of the degree of substitution up to a level of about 60%. However, a relatively high concentration of fluoride within the enamel is required for significant reduction in enamel solubility. Sub-surface enamel generally contains fluoride at levels of about 20–100 ppm, depending on fluoride ingestion during tooth development. Only the outer few micrometers of enamel can have F levels of 1,000–2,000 ppm in teeth which develop in a fluoridated water area. Even at this level there is no measurable protection against acid induced dissolution. Based on solubility data the thermodynamic solubility product constant (Ksp) of fluorapatite is only slightly less than that of hydroxyapatite. Brown et al. pointed out that this difference alone is not sufficient to account for the dramatic effects of fluoride on the acidic resistance of enamel and apatite.

The formation of lesions in shark enamel in both in vitro and intraoral models suggests that fully fluoridated apatite can also dissolve. This observation has indicated that structurally bound fluoride are not very effective in inhibiting enamel demineralization.

However, Chow suggested that F-rich mineral is still considerably more resistant to demineralization than F-poor mineral. He reported that tooth bound F in the lesion area can produce the following effects:

a) reduction of tooth mineral solubility  
b) reduction of mineral diffusion from lesion  
c) interactions between tooth-bound and ambient fluoride

The apatitically bound F can affect the concentration of calcium and phosphate and/or pH of the lesion fluid. When weak acids are present in the plaque the driving forces for diffusion of calcium and phosphate ions of the lesion fluid are decreased due to the action of tooth bound fluoride. This should lead to a reduced rate of demineralization. When only strong acids (e.g. lactic acid) are present in the cariogenic plaque, the calcium and phosphate concentrations are not lowered by tooth bound F- effect, but the pH of the lesion fluid is significantly reduced. This would decrease the rate of H+ ion diffusion into the lesion. Since H+ ions are the major driving forces for demineralization, this would also decrease the rate of demineralization.

Another important function of tooth bound F is the reduced ability of the tooth mineral to scavenge the F- in the fluids within the tooth. Fluoride rich mineral, under severe challenge, will release F- into the solution which, when the challenge becomes less severe, may promote remineralization. Takagi et al. showed that enamel resistance to lesion formation increased with increasing tooth bound fluoride content.

The caries process occurs at the enamel-plaque interference and therefore, the extracellular aqueous phase of plaque, i.e. plaque fluid, is the most relevant to the caries process. Saliva, and also plaque fluid, are supersaturated with respect to both hydroxyapatite and fluorapatite, which explains the permanent presence and stability of these apatite in the oral cavity. However, when the oral
fluids become unsaturated with respect to the apatites e.g., caused by a pH drop, a change in apatite composition may occur. In the pH range below about 5.5, the oral fluids are unsaturated with respect to hydroxyapatite, which therefore may dissolve. The low fluoride concentrations prevailing in oral fluids under physiological conditions will ensure a concurrent supersaturation with respect to fluorapatite, theoretically in the pH range of about 5.5–4.5, so that dissolution of hydroxyapatite competes with simultaneous fluorapatite or mixed fluorohydroxyapatite formation. This mechanism prevents the loss of minerals and provides additional protection of the mineral crystallites by laying fluoride rich outer layers onto the apatite crystallites. Crommelin et al. observed that fluorapatite-coated hydroxyapatite dissolved largely the same as fluorapatite, but the hydroxyapatite in a hydroxyapatite and fluorapatite mixture dissolved the same as hydroxyapatite. Therefore, significant protection could be obtained if all crystals along the acid ions diffusion pathway are coated with fluorapatite. At low pH, presumably below 4.5, the liquid phase of the plaque will be undersaturated with respect to both hydroxyapatite and fluorapatite, and no re-deposition of lost mineral (remineralization) will occur. It is reported that sound human enamel, at a pH of around 7 in the oral fluids, does not take up fluoride to a significant extent if fluoride concentrations are below 50 ppm. Living in an artificially water-fluoridated area or regularly rinsing with neutral fluoride solution does not affect the fluoride concentrations in sound enamel. Incorporation of fluoride into sound enamel is possible only as a result of concomitant enamel dissolution (caries lesion development). Therefore, these authors concluded that posteruptive maturation of erupting sound enamel, during which the enamel may be particularly susceptible to fluoride uptake, is a misnomer and most likely reflects de- and remineralization processes at a subclinical level.

Recently, it has been observed that low concentrations (up to 1 ppm) of fluoride in solution can reduce and even inhibit enamel demineralization. Ten Cate and Duijsters showed that the amount of mineral loss during demineralization is a function of both pH and fluoride concentration. When the fluoride concentration in solution is elevated the fluorapatite is correspondingly increased and it appears sufficient to prevent a caries lesion from developing. It was shown that inhibition of demineralization is a logarithmic function of the fluoride concentration in solution. The clinical implications of this would be that simply increasing fluoride concentrations might not necessarily give increased cariostatic benefit. The delivery of relatively low fluoride concentrations for longer periods should be more appropriate for enhancing clinical efficacy. Some clinical trials showed that lower fluoride concentrations than usually used in topical fluoride preparations could provide similar caries reduction. It is possible that a lower fluoride solution provides a sufficient reservoir of calcium fluoride, so that no difference in the efficacy between the two fluoride concentrations can be detected. It is conceivable that ambient fluorides provided by various F regimens may have overwhelmed the effect of tooth-bound F. Thus, efforts to increase the fluoride content of dental hard tissues by systemic or topical fluoride are not a logical approach to caries prevention. Tooth-bound fluoride can only be a supplement to ambient fluorides for greater protection.

In older studies it was claimed that the morphology of molars is affected by systemic fluoride to such an extent as to render the occlusal surfaces more resistant to bacterial invasion and demineral-
Loosely bound fluoride

In the last few years the general view is that loosely bound fluoride (CaF\(_2\)) acts as a potential »reservoir« of fluoride, enhancing remineralization and retarding demineralization processes\(^{28,37-40}\). Topical treatments with high fluoride concentrations result in the formation of calcium fluoride-like material on the surface of teeth. As early as 1945 Gerould\(^{41}\) reported that calcium fluoride was a major product on enamel when teeth were exposed to high concentrations of fluoride. It is visible by scanning electron microscope (SEM) as small globules on the surface of fluoridated teeth (Figure 1). The globular precipitates on the enamel are more homogeneous when the fluoride concentration of an applied solution is higher\(^{42}\). The globular structure of the calcium fluoride is thought to be due to incorporation of phosphate during its formation on the tooth surface\(^{43}\), since pure calcium fluoride is cubical rather than spherical. The material is described as »calcium fluoride-like«. For a long period the general view was that formation of calcium fluoride on enamel is unfavorable, because calcium fluoride is soluble in saliva to the same extent as in water\(^{26}\). The oral fluids are unsaturated with respect to calcium fluoride, thus this salt dissolves whenever it is exposed to saliva\(^{40}\). However, several studies have shown that calcium fluoride is quite insoluble in saliva at the neutral pH, and that it can persist on the tooth surface for weeks and months after topical application of fluoride\(^{44-46}\). The resistance of calcium fluoride is presumably caused by adsorption of secondary phosphate (HPO\(_4^{2-}\)) to calcium sites in the surface of calcium fluoride crystal and by pellicle proteins at neutral pH. At lower pH, as during a caries attack, primary phosphate will be the dominant phosphate ion species (HPO\(_4^{-}\)) which is unable to inhibit the dissolution of calcium fluoride. Thus fluoride ions released during cariogenic challenges are due to reduced concentration of secondary phosphate ions at acid pH. The released fluoride is subsequently built into hydroxyapatite through dissolution/re-precipitation reactions\(^{8,38}\). After caries attack, the calcium fluoride globules are again stabilized by adsorption of proteins and secondary phosphate\(^{47}\). Calcium fluoride thus constitutes a pH-controlled reservoir of fluoride on enamel. Calcium fluoride is contaminated with phosphate, not only on the surface, but also inside the crystal. This phosphate-contaminated calcium fluoride is more soluble than pure calcium fluoride and may thus release fluoride at a higher rate than pure calcium fluoride\(^{43}\). The calcium fluoride formation, its resistance in the oral environment and release of fluoride ions at low pH, explain the long-term effect of topically applied fluoride. It is suggested that the potential for formation of calcium fluoride should probably be increased in topical fluoride agents\(^{49}\). Increased time of exposure, increased concentration, lowered pH and calcium pre-treat-
ment have proved to be effective means of increasing calcium fluoride deposition on enamel in vitro.

CaF$_2$ can be formed on intact enamel and be covered with plaque, on and in demineralized enamel, or in plaque. The reactivity of fluoride on sound enamel and carious enamel differs significantly. Carious enamel is more reactive with fluoride than sound enamel. Carious enamel acquires more fluoride, acquires it faster, and acts as a source of retained fluoride in comparison with the more limited reactivity of sound enamel. Ten Cate and Loveren hypothesized that different morphology of a calcium fluoride deposit in the lesion pores may result in more effective inhibition than the fluorapatite growing on the existing hydroxyapatite crystallites. However, no data described the dissolution kinetics of calcium fluoride formed in inaccessible pores of natural lesions. It could be expected that the dissolution period is much longer. Another interesting observation is that a continuous layer of small particles of calcium fluoride may cover the enamel completely and protect it to a higher degree than fluorapatite, because the solubility of calcium fluoride is less pH dependent than fluorapatite. Thus the preparations of fluoride with low pH produce pure or almost pure calcium fluoride which may protect the enamel surfaces. Koulourides demonstrated that acid-softened enamel, rehardened by fluoridation, acquired significant secondary resistance to acid attack, developing so-called "acquired resistance". The acquired fluoride enhances both remineralization and demineralization resistance.

Overall, it is clear that both fluorapatite and calcium fluoride can provide $F^-$ to the solution phase and enhance remineralization and retard demineralization of enamel hydroxyapatite crystallites. The fluorapatite provides most $F^-$ under low pH conditions, while CaF$_2$ provides $F^-$ at neutral or lower pH. The fluoride, present in the solution from topical sources, enhances remineralization by speeding up the growth of a new surface on the partially demineralized subsurface crystals in the caries lesion. Thus, the fluorapatite probably has limited value in caries prevention, whereas the remineralization process as such may be crucial. This supports the hypothesis that permanent fluoride ion activity during a caries process is more important than a high content of fluoride in the enamel.

The Antimicrobial Action of Fluoride

In spite of extensive literature on the antimicrobial effects of fluoride on oral microflora, today there is very little consensus that the anticaries effect of fluoride is related to inhibition of oral bacteria.

Early studies showed the inhibitory effect of fluoride on pH fall or acid production in plaque after a sucrose or glucose challenge. Initially, it was postulated that fluoride may be released from the enamel surface at low pH in sufficient concentrations to interfere with glycolitic enzymes and to prevent further increase in hydrogen ion concentration. However, more recent studies suggest that fluoride present in the surface enamel does not significantly prevent acid production. The concentrations of fluoride present in the saliva are too low to affect bacterial metabolism. On the other hand, appreciable amounts of fluoride may accumulate in dental plaque. However, fluoride concentrations needed for antimicrobial effects surpass significantly the concentrations which can reduce the solubility of apatite. Since less than 1 ppm of fluoride will cause rapid precipitation of fluorapatite from high concentrations of calcium and phosphate present in the plaque it is unlikely that fluoride inhibition of bacterial production in plaque is of any significance. This is an important argument in debates on the effect of
fluoride in dental plaque and its contribution to caries prevention.\(^{51}\)

In order to provoke any antimicrobial effect fluoride has to enter the bacterial cell. Fluoride diffuses into cariogenic bacteria in the form of HF (a weak acid, pKa 3.15). At the lower external pH, more HF is formed and more of it diffuses into the cell. Once inside the cell the HF dissociates into H\(^+\) and F\(^-\), because of a higher internal pH of cells, such as oral streptococci, than external. This continued diffusion and dissociation leads to the accumulation of fluoride in the cell and the acidification (accumulation of H\(^+\)) of the cytoplasm. The result is a reduction in both the proton gradient and the enzyme activity. Current information indicates that fluoride ions within the cell interfere with the glycolytic enzyme (enolase) activity and proton-extruding adenosine triphosphatase (H\(^+\)/ATP -ase), which is involved in the generation of proton gradients through the efflux of protons from the cell at the expense of ATP.\(^{56}\) Thus, fluoride inhibit effectively the carbohydrate metabolism of acidogenic oral bacteria, including the uptake of sugars.\(^{51}\) In spite of these known effects, there is no general agreement that the antimicrobial effects of F contribute to the anticaries effect of fluoride.\(^{56}\)

Many investigators tend to dismiss the role of fluoride in the metabolic activity of bacteria, on the grounds that only large concentrations are effective, and that there are no differences in the Streptococcus mutans populations in persons residing in fluoridated and in non-fluoridated areas.\(^{57}\) In addition, the widespread use of toothpastes, which have been responsible for the decrease in caries prevalence over the last three decades, did not result in a reduction in the number of the mutans streptococci.\(^{58}\) White et al.\(^{59}\) suggested that topical fluoride from the over-the-counter dentifrice affects only minimal reductions in acute plaque metabolic activity (acid production). Van Loveren\(^{58}\) summarized the antimicrobial action of fluoride and suggested that the continuous daily application of fluoride reduces the acidogenicity of plaque, although there is no direct link with clinical inhibition of caries. A single application of professionally applied topical fluoride at a high concentration, although transient, reduces the plaque’s ability to produce acid, but has little clinical significance in controlling dental caries.

Adaptation of Streptococcus mutans to fluoride has been suggested as the reason for the reduced cariogenic potential of the bacterial cells. Possible adaptation of streptococci in dental plaque to frequent exposure to fluoride will not necessarily decrease the caries preventive effects caused by topically applied fluoride agents (i.e. fluoride lacquer).\(^{60}\) Van Loveren et al.\(^{61}\) showed that the use of fluoride toothpaste does not affect plaque composition, or fluoride tolerance or acidogenicity of mutans streptococci. In general, the clinical contribution fluoride “anti-plaque” effects to caries is poorly understood.\(^{62}\)

Recommendations for the Future Use of Fluoride

Two theories of the cariostatic mechanism of fluoride are suggested in caries prevention. One stresses the importance of an ample supply of fluoride during tooth formation, and the other a lifelong daily supply. Larsen\(^{63}\) pointed out, that the two theories may complement each other, and neither of the theories excludes the other. On the basis of present information, it is suggested that the post-eruptive effect of fluoride is by far the most important. There is considerable evidence to suggest that low concentrations of fluoride decrease the rate of demineralization and enhance the rate of remineralization. Thus, the effectiveness of fluoride as a cariostatic agent depends on the availability of free fluoride in plaque during cariogenic challenge, i. e. during
acid production. The most effective caries preventive effect of fluoride is frequent (daily) application of low fluoride from toothpastes and (or) mouthrinses. Thus, this basic fluoride prevention should be encouraged in all patients. The need for additional fluoride supplementation depends on caries activity. The formation of intraoral reservoirs capable of supplying ions for a prolonged period is crucial for the success of topical treatments. Fluoride which is retained on the teeth after brief exposure to topical fluoride agents or toothpastes is retained as calcium fluoride. Calcium fluoride is most likely the provider of free ions during cariogenic ride. Calcium fluoride is most likely the fluoride effect.

REFERENCES

The quality of oral hygiene is essential in relation to topical fluoride application. The limit of fluoride effect is reached when pH drops so low that even the solubility product of pure fluorapatite is not exceeded. If the oral hygiene is inadequate, accumulation of thick, acidogenic plaque at retention sites will occur. In patients with heavy plaque, the pH reaches, during an acid challenge, values far below the critical pH. In such conditions the beneficial effects of fluoride would also be limited.

The combination of proper oral hygiene and the use of fluoride therapy can, in most cases, arrest the caries process. In addition, improved new remineralizing therapies, using topical treatments to replace lost calcium and phosphate mineral from early caries lesions would be a promising additional caries preventive mechanism, supporting and increasing the fluoride effect.

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Tumačenje antikarijesnog mehanizma djelovanja fluorida

S A Ž E T A K