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# Fluorides – Mode of Action and Recommendations for Use

**Summary** Various authors have shown that the caries decline in the industrialized countries during recent decades is based on the use of fluorides, of which local fluoride application in the form of fluoridated toothpastes is of primary importance. The caries-protective potential of fluorapatite is quite low; in contrast, dissolved fluorides in the vicinity of enamel are

effective both in promoting remineralization and inhibiting demineralization. Considering the fact that the caries decline occurred at the same time that local fluoridation measures became widely used, the conclusion seems justified that regular application of F<sup>-</sup> can inhibit caries.

## Introduction

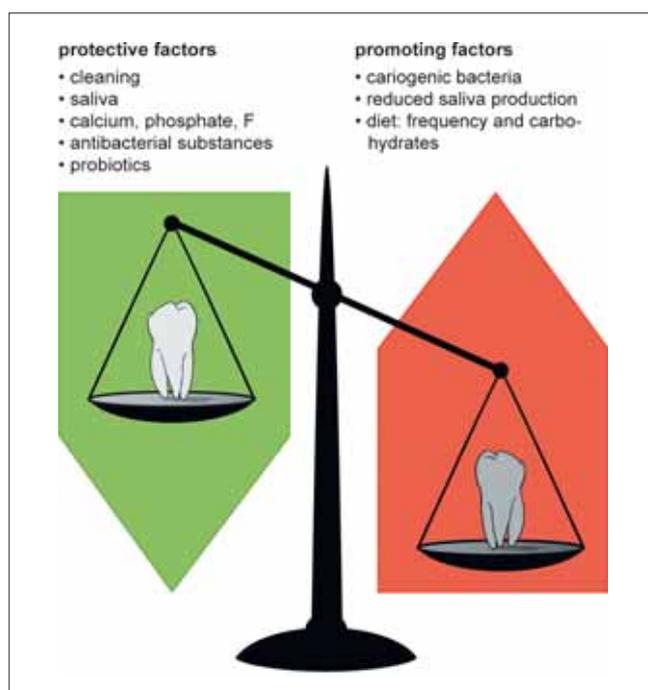
Dental hard tissue consists of highly mineralized enamel, as well as dentin and cementum, which contain a much greater proportion of organic matrix. The mineral phase of the dental hard tissues is not pure hydroxyapatite (HAP = Ca<sub>10</sub>(PO<sub>4</sub>)<sub>6</sub>OH<sub>2</sub>), but rather is a calcium-deficient biomaterial in which numerous other ions are incorporated. Building hydrogen phosphate, carbonate and magnesium ions into the HAP lattice leads to a less stable, more soluble apatite. The greater proportion of carbonate in dentin (5.5%) than in enamel (3%) makes dentin crystals more susceptible to acid attack. However, the partial substitution of fluoride ions for OH groups in the crystal lattice can stabilize the apatite structure to a certain degree.

In healthy human enamel, fluorhydroxyapatite (FHAP) or fluorapatite (FAP) are present in addition to HAP, although in the outermost enamel layer, less than an average of 5% of the OH groups of HAP are replaced by fluoride. At a depth of 50 μm, this percentage drops further.

The present article discusses the importance of fluoride for caries prevention (FEATHERSTONE 2000, LUSSI 2010) (Fig. 1) and presents practical recommendations for the use of fluoride.

## Acid attack

Enamel is a calcium-deficient, carbonate-rich hydroxyapatite. In its stable state, there are sufficient Ca<sup>2+</sup>, PO<sub>4</sub><sup>3-</sup>, OH<sup>-</sup> and F<sup>-</sup>



**Fig. 1** The caries balance. Pathological and protective factors which shift the caries balance between de- and remineralization (modified from Featherstone 2000)

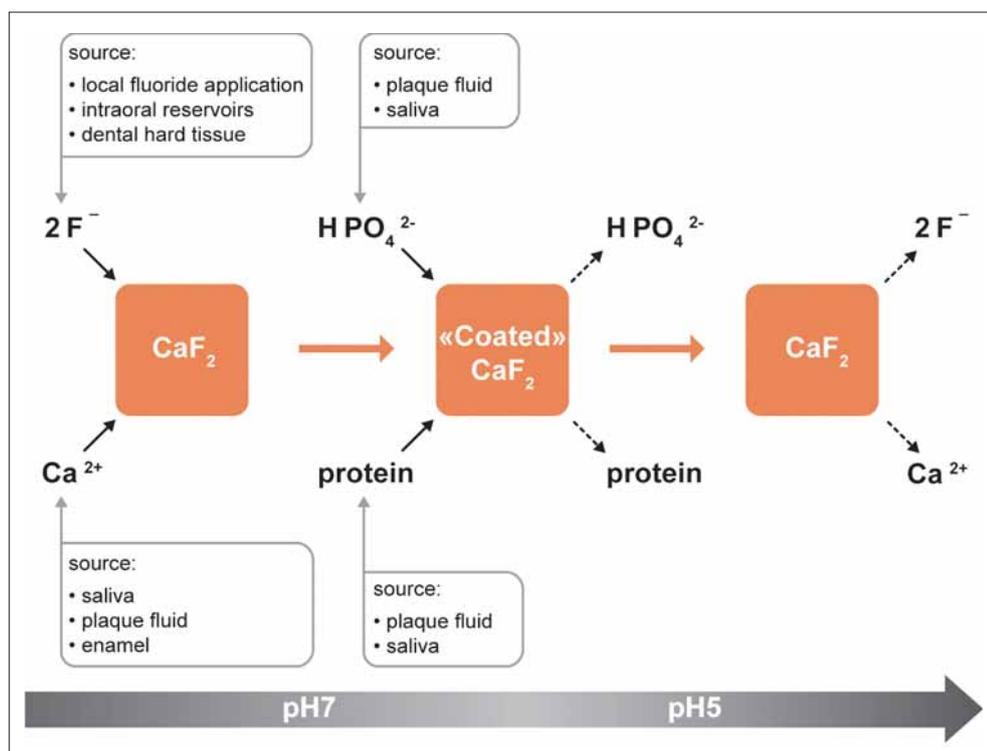


Fig. 2 Formation and decomposition of calcium-fluoride-like material (modified from RÖLLA & SAXEGAARD 1990).

ions in the immediate vicinity of the crystals to maintain an equilibrium with the surrounding fluid.

The (active) concentrations (activities) of these ions determine the degree of saturation of the solution. The latter then determines whether HAP dissolves (“undersaturation”) or deposits minerals from the environment in the enamel (“supersaturation”). During cariogenic acid attack, plaque bacteria form organic acids from carbohydrates; as the acids dissociate,  $H^+$  ions are released. The increased  $H^+$  concentration (low pH value) in the plaque fluid surrounding the tooth decreases the  $OH^-$  concentration. In addition, the  $H^+$  ions protonate phosphate ions ( $PO_4^{3-}$ ) in the plaque fluid to  $HPO_4^{2-}$  and especially to  $H_2PO_4^-$  (DAWES 2003). Because the  $PO_4^{3-}$  concentration decreases at low pHs, phosphate ions ( $PO_4^{3-}$ ) and later hydroxyl ions ( $OH^-$ ) dissolve out of the tooth in order to maintain the solution’s equilibrium at the vicinity of surface. This process – also to maintain neutrality – finally leads to the release of calcium from hard tooth substance, i. e., the tooth dissolves (DAWES 2003).

The dynamic of this dissolution process depends not only on the composition of the enamel, dentin and cement crystals but also on the plaque surrounding the tooth. This situation explains both the different critical pH values for enamel (ca. 5.5) and dentin (ca. 6.3), and to a certain extent the variations in caries activity between patients, because the calcium, phosphate or fluoride content of the saliva and plaque can vary from patient to patient. The frequency of sugar consumption and lack of oral hygiene influence these factors and play an even more important role.

Erosions arise when plaque-free teeth are chronically exposed to endogenous or exogenous acids. In the process of erosion, not just the pH value alone is important but also the calcium, phosphate and fluoride content of the erosive beverage contacting the tooth. For this reason, the “critical” pH value for erosion can be much lower if the beverage or food contains added calcium.

## The inhibition of demineralization by fluoride

Numerous studies have comprehensively documented that the incorporation of fluorides into the mineral components of enamel only slightly reduces its solubility (ARENDS & CHRISTOFFERSEN 1986, TEN CATE & DUIJSTERS 1983). Small amounts of fluoride in solution around the tooth inhibit demineralization more effectively than incorporated fluoride and have a much greater caries-protective potential than a large proportion of FAP in enamel mineral. In a fundamental experimental approach, OGAARD ET AL. (1988) used shark dental enamel, which almost completely consists of pure FAP. In comparison, healthy human enamel contains considerably less  $F^-$ , which is primarily located in the outermost layer. In shark enamel, which has a fluoride content of 32000 ppm, approximately 99% of the  $OH^-$  sites are replaced by  $F^-$ , whereas in human enamel, this is the case at less than 5% of the  $OH^-$  sites. In the in-situ part of the study mentioned above (OGAARD ET AL. 1988), shark and human enamel were mounted in a removable appliance which was also equipped with plaque-retentive elements. In both shark and human enamel, carious lesions developed, although lesion depth was somewhat less in shark enamel. Another part of the study showed that mineral loss in human enamel was even lower than in shark enamel when the participants rinsed daily with a 0.2% NaF solution. The hypothesis was thus confirmed that free fluoride ions in solution around the tooth or enamel crystals play a much more important role in caries prevention than fluorides incorporated in the enamel crystals themselves. Under these conditions, fluoride ions are in part adsorbed onto the crystalline surface and are in dynamic equilibrium with the fluoride ions in solution in the immediate vicinity. In the fluid surrounding the crystals, this leads to an equilibrium or supersaturation relative to fluor(hydroxy)apatite and hence to reprecipitation of minerals. In addition, the adsorption of fluoride on the crystals is thought to offer direct protection from demineralization. In (fluoride) unprotected

areas, however, enamel crystals can be locally dissolved during an acid attack. These low fluoride concentrations are also attained after consuming foods containing fluoridated table salt, since the  $F^-$  content of saliva significantly increases for about 30 minutes after such meals (HEDMAN ET AL. 2006). It can be inferred that fluoridated drinking water and table salt also function according to this mechanism, since the formation of  $CaF_2$  at these low concentrations and at this pH is unlikely.

## Calcium fluoride ( $CaF_2$ )

Calcium fluoride is considered an important factor for caries prevention (Fig. 2), or to be more precise, a calcium fluoride-like material. It precipitates on the tooth's surface when compounds containing  $F^-$  are applied. The calcium originates either from saliva or in part also from the tooth after application of slightly acidic fluoride solutions (SAXEGAARD & RÖLLA 1989, LARSEN & RICHARDS 2001). Because this precipitate can be dissolved from the enamel surface with potassium hydroxide without negatively influencing the fluoride structurally incorporated in the enamel mineral, it is also termed KOH-soluble fluoride (CASLAVSKA ET AL. 1975).

In vitro, the short-term application of neutral fluoride preparations leads to the formation of only very low amounts of  $CaF_2$ . However, much greater amounts are found when the enamel has been altered by initial caries lesions (HELLWIG ET AL. 1987, BRUUN & GIVSKOV 1991). In systematic examinations, SAXEGAARD & RÖLLA (1988) found an increase in  $CaF_2$  formation by decreasing the pH of the fluoride solution, increasing the  $F^-$  concentration, prolonging the exposure times, etching the enamel surface, and making additional calcium available. In vitro, calcium fluoride is only formed at fluoride concentrations of at least 300 ppm when solutions with a neutral pH are applied. In contrast, at pH 5, a concentration of 100 ppm fluoride is sufficient to initiate spontaneous precipitation of calcium fluoride (LARSEN & JENSEN 1994). These findings provide the foundation for attempts to develop means of local fluoridation which will lead to  $CaF_2$  formation on tooth surfaces after relatively brief contact.

In SEM observations,  $CaF_2$  appears as spherical globules, the morphology of which can vary in terms of amount and size. Using an acidic aminefluoride solution, the first  $CaF_2$  globules already form after 20 seconds, using acidic sodium fluoride somewhat later, and using sodium monofluorophosphate (MFP),  $CaF_2$  does not form at all in vitro (PETZOLD 2001). Because the fluoride in MFP is covalently bound, it must first be released in the oral cavity by hydrolysis before it can react with calcium. Thus, after applying a low-dosage aminefluoride dentifrice (250 ppm), HELLOWIG ET AL. (1990) found considerable amounts of KOH-soluble fluoride on the enamel, but not after applying a toothpaste containing MFP. This facilitation of  $CaF_2$  formation by low pH was confirmed in an in-situ study comparing a neutral-pH toothpaste containing sodium fluoride with an aminefluoride-containing toothpaste of pH 5.5. After 4 weeks of application,  $CaF_2$  formation on enamel was markedly higher with the aminefluoride toothpaste (KLIMEK ET AL. 1998)

Pure  $CaF_2$  does not form in vivo, because phosphates, proteins and other substances are deposited on it. This stabilizes the precipitate and makes it more resistant to acids. The stability is chiefly due to the adsorption of hydrogen phosphate ions  $HPO_4^{2-}$  on the surface of the  $CaF_2$  crystals, giving rise to a solubility-inhibiting protective film. During a carious attack,  $F^-$  ions are released from the  $CaF_2$  depot due to the reduced  $HPO_4^{2-}$  ion concentration at acidic pHs. Hence,  $CaF_2$  functions

as a pH-driven  $F^-$  reservoir, which releases  $F^-$  at low pHs during an acid attack and remains stable longer on the enamel surface at neutral pHs (RÖLLA & EKSTRAND 1996). Based on these mechanisms,  $CaF_2$  is considered the main source of free  $F^-$  ions during acid attacks. The  $F^-$  ions released both inhibit demineralization and promote remineralization. During a carious attack, they are substantially more important than a high  $F^-$  content of the enamel crystals (FEJERSKOV ET AL. 1981).

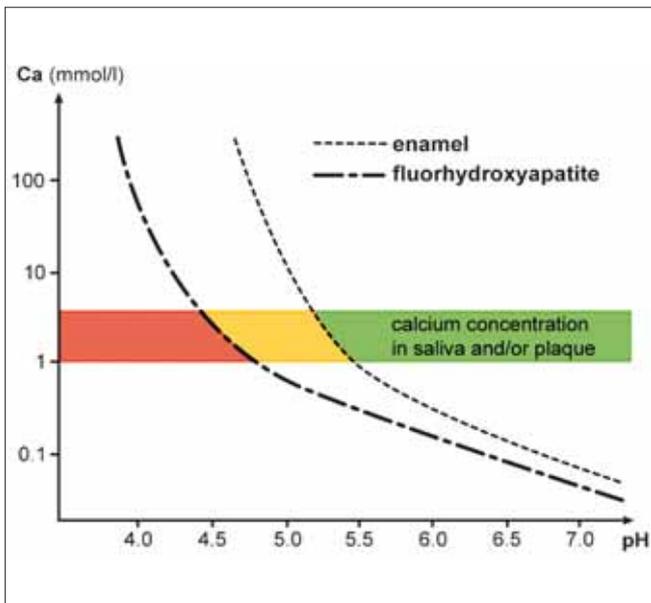
Because saliva is undersaturated with respect to  $CaF_2$ , the  $CaF_2$  film exists only relatively briefly. Most of it is lost already just a few hours or days after fluoridation. In contrast, after application of highly concentrated fluoride solutions preceded by enamel etching, CASLAVSKA ET AL. (1991) still found substantial amounts 6 weeks later in enamel biopsies, with small amounts of  $CaF_2$  detectable even after 18 months. After a single application of a concentrated local fluoride, ATTIN ET AL. (1995) observed an 80% loss of  $CaF_2$  after 5 days in situ. Nevertheless, in this and other studies, a simultaneous increase in the structurally bound fluoride in initial enamel lesions was also apparent (HELLWIG ET AL. 1989, BUCHALLA ET AL. 2002). The dissolution of the  $CaF_2$  film also leads to a caries-prophylactically relevant increase in the fluoride concentration of saliva and plaque. This was shown in a study by ISSA & TOUMBA (2004), where 2 hours after applying an aminefluoride or sodium fluoride toothpaste, an increased fluoride concentration was still evident in saliva. If, after professional tooth cleaning, the teeth are coated with  $CaF_2$ -forming fluoride preparations, the plaque which forms later exhibits more  $F^-$  and thus provides better protection from demineralization (TENUTA ET AL. 2008).

Calcium fluoride is certainly the most important and possibly even the only reaction product on the dental hard tissues after local application of fluoridation media (RÖLLA ET AL. 1993). It is equally certain that the protective calcium-fluoride-containing film coating the enamel – from which fluoride is released, depending on pH – plays a particularly important role in the caries-prophylactic effect of fluoride.

## Promoting remineralization by fluoride

At a neutral pH of 7, low ion concentrations are sufficient to keep dental hard tissues in equilibrium. If the pH drops due to acid production by the plaque, higher ion concentrations are necessary to prevent dissolution. At a pH of ca. 5.5, undersaturation begins, that is, the calcium- and phosphate-ion concentrations in the plaque fluid are not sufficient to maintain the enamel in stable equilibrium; thus, the enamel starts to dissolve (Fig. 3 yellow and red area). In contrast, fluorhydroxyapatite (FHAP) and fluorapatite (FAP) remain stable even at lower pHs; for these two minerals, undersaturation and subsequent dissolution begin at a pH of around 4.7. With increasing pH, supersaturation with respect to FHAP begins first, which means that during remineralization FHAP and FAP form first as long as fluoride is present in the oral cavity. Consequently, during remineralization after acid attack, a redistribution of mineral phases occurs, in which the proportion of stable, carbonate-poor FHAP in the enamel increases at the expense of carbonate-rich HAP. Because of this, demineralized and subsequently remineralized dental enamel is somewhat more acid resistant than undamaged enamel. During remineralization, the contribution of saliva with  $Ca^{2+}$ ,  $PO_4^{3-}$  and  $OH^-$  ions in addition to the presence of dissolved  $F^-$  is important.

To summarize, because of its low solubility product, fluorhydroxyapatite forms more rapidly even in slightly acidic milieus than do the other calcium phosphate phases, which



**Fig. 3** Solubility curves for enamel and fluorhydroxyapatite (modified from LUSSI 2010).

means that fluoride accelerates and promotes remineralization.

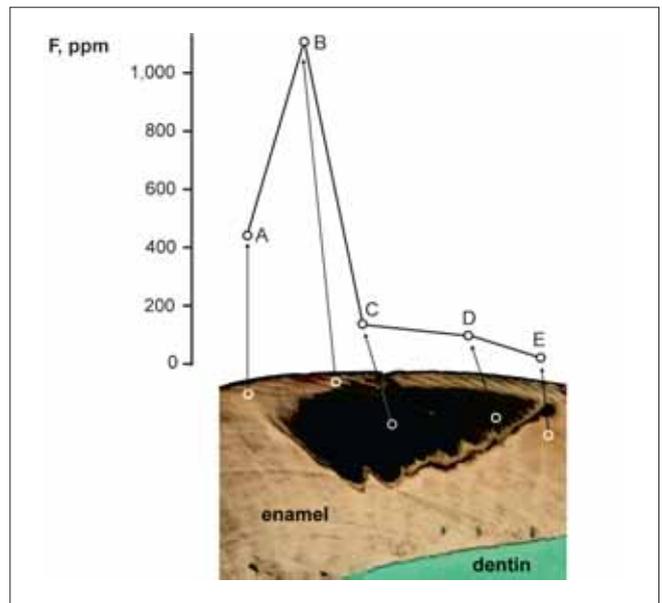
The fluoride content of healthy enamel is lower than in an initial (white-spot) lesion, since the latter has already undergone many de- and remineralization phases. Figure 4 depicts the various regions of a white-spot lesion. In the superficial area (B), WEATHERELL ET AL. (1977) found dramatically increased  $F^-$  concentrations of over 1100 ppm, whereas in healthy enamel surfaces (A) just 450 ppm were detected. Towards the center of the lesion (C), the fluoride concentration dropped to about 150 ppm, as in deeper enamel layers, where the fluoride concentration was only ca. 100 ppm. Thus, compared to pure fluorapatite, healthy enamel has incorporated approximately 2% fluoride. Under optimal remineralization conditions, this value can increase in the surface of an initial caries lesion.

The increased fluoride concentration in the superficial region of a white-spot lesion is partly based on fluoride-promoted remineralization, i. e., on the formation of fluoride-rich apatite, and partly on increased  $F^-$  intake due to the porous surface of the white spot (HALLSWORTH ET AL. 1975). When fluoride is present, demineralized crystals serve as nuclei for the accumulation of new mineral. As described above, fluoride accelerates this process, because remineralization is already possible at lower pHs. The result is a fluoride-rich, carbonate-poor, acid-resistant surface mineral layer (Fig. 5). For these reasons, initial caries lesions should not be operatively removed.

In this context, it is worth mentioning that dentin demands a considerably higher fluoride concentration in its surrounding solution than enamel does to reach an equivalent degree of demineralization inhibition. This is important in root-caries prevention. BAYSAN ET AL. (2001) demonstrated that a high-fluoride toothpaste (5000 ppm) used at least daily remineralized initial root caries lesions.

### Antimicrobial effect of fluorides

In the laboratory, it was shown that the carbohydrate metabolism of oral streptococci and lactobacilli can be inhibited by fluoride (BALZAR ET AL. 2001). Particularly at low extracellular



**Fig. 4** Fluoride content of healthy enamel and different areas of a white spot (initial lesion) (modified from WEATHERELL ET AL. 1977)

pHs, fluoride is transported as HF into the bacterial cell, where it then dissociates into  $H^+$  and  $F^-$  (LI & BOWDEN 1994). This process leads to an accumulation of fluoride inside the cell and simultaneously to an over-acidification of the cytoplasm. In the cell, fluoride can inhibit two enzymes: enolase and the proton-releasing adenosine triphosphatase (SUTTON ET AL. 1987). The over-acidification of the cytoplasm can also inhibit the mechanism of glucose transport into the cell. Although these mechanisms have been relatively reliably proven in simple cell cultures, there is still no proof that this antimicrobial effect of fluoride contributes to caries prevention, as it is possible that the fluoride concentrations in the oral cavity are too low to exert a prophylactic effect (TEN CATE & VAN LOVEREN 1999).

Another mechanism which has been discussed is the interference in bacterial adhesion to the tooth's surface after pretreatment with fluoridated compounds (VAN DER MEI ET AL. 2008). However, discrepant results have been reported. Although some studies demonstrated that bacterial adhesion and in part also bacterial metabolism are impaired by such pretreatment, other studies found no difference between untreated and treated enamel. Nevertheless, there is some indication that cations of fluoride compounds – e. g., stannous or amine components – can impair bacterial colonization (VAN DER MEI ET AL. 2008). Contradictory results have also been reported on the effect of fluorides on plaque composition. On the one hand, it was shown that under the influence of fluorides, the number of Mutans streptococci decreased; on the other hand, other studies found no difference in the plaque composition of people living in areas with highly fluoridated drinking water vs. those in areas where the drinking water contained little fluoride (KILIAN ET AL. 1979). In addition, the widespread use of fluoride toothpaste has not changed the number of Mutans streptococci in plaque. At this juncture, it should be noted that even in acidic fluoride compounds, only a small proportion is present as HF. The pK value of hydrofluoric acid is 3.14, which means that at this pH, half of the acid is present as HF and half as  $F^-$ . At a pH of 5, only about 1% exists as HF and the rest as free fluoride. Such low pH values are only expected on the tooth's surface for very short periods.

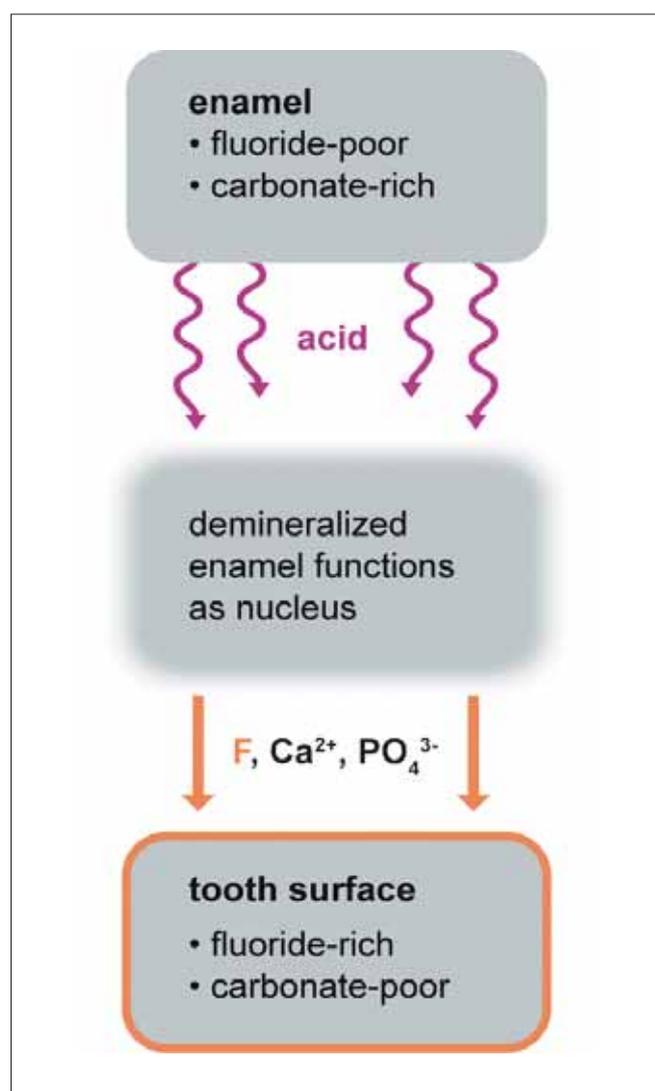


Fig. 5 Overview of de- and remineralization processes (modified from FEATHERSTONE 2000).

For many years, it was thought that certain bacterial species could adapt to continual exposure to fluoride and that the potentially caries-preventive effect of fluoride would therefore be lost. Upon closer examination, however, it was found that this adaptation leads to decreased acidogenicity of human plaque; thus, the anticariogenic effect is instead maintained (TEN CATE & VAN LOVEREN 1999).

Overall therefore, it can be said that the caries-preventive effect of fluorides can only be very slightly attributed to an effect in the oral biofilm, if at all.

### Caries-reducing efficacy and fluoride recommendations

The caries-prophylactic effect of locally applied fluoride compounds has been emphasized in numerous systematic review articles (MARINHO ET AL. 2002a, b, MARINHO ET AL. 2003a, b, c, MARINHO ET AL. 2004a, b, WALSH ET AL. 2010). Only scarce evidence from clinical studies exists on the use of fluoride tablets. The available information recommending fluoride tablets assumes that they are locally effective on erupted teeth. In agreement with other, older reviews, a recent review article (ROZIER ET AL. 2010) states that fluoride tablets should only be prescribed

for children who have a high caries risk and who do not regularly use other means of fluoridation (e. g., fluoridated drinking water, fluoridated table salt, fluoride toothpaste). If the tablets are used at all, they should be used regularly by sucking/letting dissolve in the mouth. Because the effect of fluorides is predominantly local on the tooth, prescription of fluoride tablets is now rare or has been discontinued in most countries.

The body of evidence for table-salt fluoridation is also rather weak (YENGOPAL ET AL. 2010). However, it may be assumed that table-salt fluoridation is an effective caries-preventive measure, although in countries which already have a high level of caries prevention, the additional effect of fluoridated table salt is hardly quantitatively detectable.

Daily use of fluoride toothpaste forms the foundation of caries prophylaxis with fluorides, as it is readily available and, when used regularly, continually provides fluoride ions for caries-protective processes on the tooth's surface. This caries-prophylactic effect is evident in all age groups (MARINHO ET AL. 2003a, c) and increases with increasing fluoride concentration (Walsh ET AL. 2010). Several studies have shown that children's toothpastes with a fluoride content of 500 ppm are also effective in terms of preventing caries (STOOKEY ET AL. 2004, LIMA ET AL. 2007). Especially in countries where other means of fluoridation are implemented (e. g., table salt, drinking water), only children's toothpaste should be used in children up to age 6 in order to prevent fluorosis caused by excess fluoride ingestion, despite a recent Cochrane review to the contrary, which recommends toothpaste with a fluoride content of 1000 ppm and more (WALSH ET AL. 2010). Furthermore, it is known that the effect of fluoride toothpaste increases with more frequent toothbrushing (MARINHO ET AL. 2003a). In addition, professionally applied fluoride compounds, such as varnishes or gels, are recommended especially where the caries risk is high (MARINHO ET AL. 2003a, b). Applied four times per year, this contributes to an improved caries-preventive effect.

Fluoride gels can also be individually brushed on once a week. Systematic reviews show that this reduces caries to a similar extent as quarterly application by a dental professional (MARINHO 2002a). Fluoridated mouthwashes should first be given to children when they are old enough for school, and then only if an increased caries risk exists (MARINHO ET AL. 2003b). However, fluoridated mouthwashes are recommended for patients wearing fixed orthodontic appliances (OGAARD ET AL. 2006). A randomized, prospective, clinical study also showed that the supervised use of fluoridated mouthwashes in adolescents led to a lower incidence of caries in the approximal area compared to a control group (MOBERG SKÖLD ET AL. 2005). Studies from the 1990s found 20% more caries in those who rinsed thoroughly after brushing (CHESTERS ET AL. 1992, SJÖGREN & BIRKHED 1993, O'MULLANE ET AL. 1997) than in those who used other rinsing methods. However, a later prospective study with monitored toothbrushing showed that rinsing did not have the negative influence assumed previously (MACHIULSKIENE ET AL. 2002). The same situation was shown for approximal caries prophylaxis. With the recommendation to rinse with a small amount of water, a caries reduction was obtained while also spitting out most of the toothpaste with its numerous additives. Further studies are necessary to make a definitive, general recommendation on rinsing for all ages. Figure 6 illustrates the recommendations on fluoride application. In this form, they constitute the basis of the German and Swiss fluoridation guidelines. In caries-active children, children's toothpaste can be started twice a day at an earlier timepoint than indicated in the guidelines.

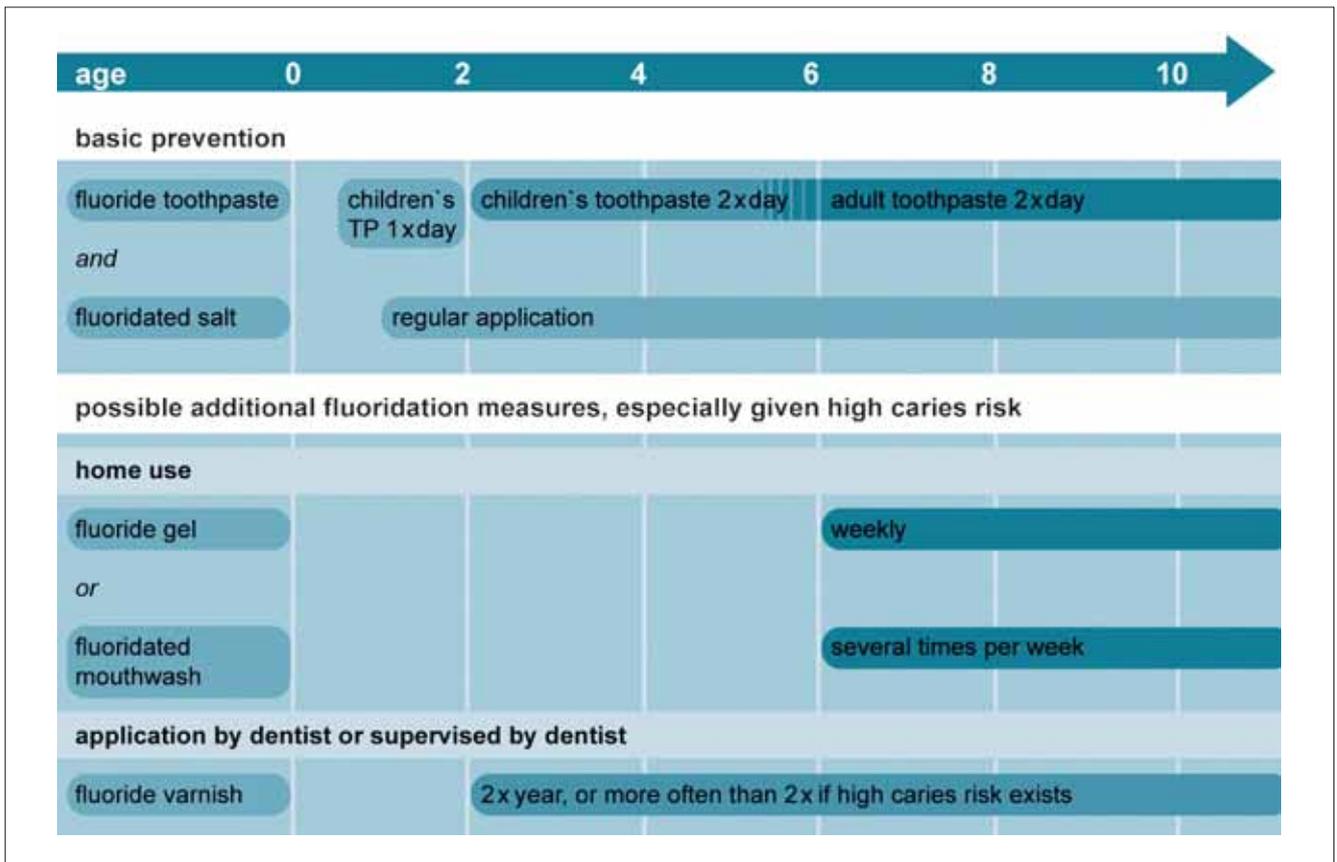


Fig. 6 Recommendations for fluoride use.

In 2005, the European Food Safety Authority (EFSA) determined that fluoride is not an essential trace element for human growth and development. In an official statement on the fluoridation of drinking water, the Scientific Committee on Health and Environmental Risks (SCHER) of the European Commission also wrote that although the scientific evidence for the protective effect of locally applied fluoride is strong, the data supporting systemic application are less convincing. It is notable that only part of the caries decline in schoolchildren observed in Switzerland can be explained by fluoridation measures (STEINER ET AL. 2010). Finally, the Guidelines of the American Academy of Pediatrics (AAP) recommend supervised toothbrushing with fluoride toothpaste for all children who have at least one erupted tooth.

Fluoride is, of course, no miracle cure; neither is caries a fluoride-deficiency disease. This explains why the efficacy of fluoridated compounds decreases with increasing caries activity. Thus, in children and adults with high caries risk, further measures are necessary, such as improving oral hygiene, nutrition counseling and guidance, as well as regular dental check-ups. As in many other diseases, however, social factors are also

at work in cariogenesis. The political responsibility is thus given to establish appropriate conditions that facilitate good education and an adequate social environment, especially for children.

## Résumé

Plusieurs auteurs ont démontré que la réduction de la carie dans les pays industrialisés durant les dernières décennies repose sur l'application de fluorure. Cependant, c'est surtout l'application locale de fluorure et principalement l'usage de pâte dentifrice fluorée qui sont d'importance majeure. L'apatite de fluorure a un faible potentiel de protection contre la carie, alors que les fluorures faiblement liés dans l'environnement de l'émail sont non seulement actifs dans la promotion de la reminéralisation, mais aussi dans l'inhibition de la déminéralisation. Si nous comparons la réduction de caries dans le même laps de temps que l'utilisation répandue de dispositifs de fluoridation topique, il est tout à fait justifié de conclure que l'application régulière de fluorures a un effet cariostatique.

## References

- ARENDTS J, CHRISTOFFERSEN J: The nature of early caries lesions in enamel. *J Dent Res* 65: 2–11 (1986)
- ATTIN T, HARTMANN O, HILGERS R D, HELLMIG E: Fluoride retention of incipient enamel lesions after treatment with a calcium fluoride varnish in vivo. *Archs Oral Biol* 40: 169–174 (1995)
- BALZAR EKENBÄCK, S, LINDER L E, SUND M L, LÖNNIS H: Effect of fluoride on glucose incorporation and metabolism in biofilm cells of streptococcus mutans. *Eur J Oral Sci* 109: 182–186 (2001)
- BAYSAN A, LYNCH E, ELLWOOD R, DAVIES R, PETERSSON L, BORSBOMM P: Reversal of primary root caries using dentifrices containing 5000 and 1100 ppm fluoride. *Caries Res* 35: 41–46 (2001)
- BRUUN C, GIVSKOV H: Formation of CaF<sub>2</sub> on sound enamel and in caries-like lesions after different forms of fluoride application in vitro. *Caries Res* 25: 96–100 (1991)
- BUCHALLA W, ATTIN T, SCHULTE-MÖNING J, HELLMIG E: Fluoride uptake, retention, and remineralization efficacy of highly concentrated fluoride solution on enamel lesions in situ. *J Dent Res* 81: 329–333 (2002)
- CASLAVSKA V, MORENO E C, BRUDEVOLD F: Determination of the calcium fluoride formed from in vitro exposure of human enamel to fluoride solutions. *Arch Oral Biol* 20: 333–339 (1975)
- CASLAVSKA V, GRON P, KENT R L, JOSHIPURA K, DEPAOLA P F: CaF<sub>2</sub> in enamel biopsies 6 weeks and 18 months after fluoride treatment. *Caries Res* 25(1): 21–26 (1991)
- CHESTERS R K, HUNTINGTON E, BURCHELL C J, STEPHEN K W: Effect of oral care habits on caries in adolescents. *Caries Res* 26: 299–304 (1992)
- DAWES C: What is the critical pH and why does a tooth dissolve in acid? *J Can Dent Assoc* 69(11): 722–724 (2003)
- FEATHERSTONE J D B: The science and practice of caries prevention. *JADA* 131: 887–889 (2000)
- FEJERSKOV O, THYLSTRUP A, LARSEN M J: Rational use of fluorides in caries prevention. A concept based on the possible cariostatic mechanisms. *Acta Odontol Scand* 39: 241–249 (1981)
- HALLSWORTH A S, WEATHERELL J A, ROBINSON C: Fluoride uptake and distribution in human enamel during caries attack. *Caries Res* 9: 294–299 (1975)
- HEDMAN J, SJÖMAN R, SJÖSTRÖM I, TWETMAN S: Fluoride concentration in saliva after consumption of a dinner meal prepared with fluoridated salt. *Caries Res* 40: 158–162 (2006)
- HELLMIG E, KLIMEK J, WAGNER H: The influence of plaque reaction mechanism of MFP and NaF in vivo. *J Dent Res* 66: 46–49 (1987)
- HELLMIG E, KLIMEK J, ALBERT G: In-vivo Retention angelagerten und festgebundenen Fluorids in demineralisiertem Zahnschmelz. *Dtsch Zahnärztl Z* 44: 173–176 (1989)
- HELLMIG E, KLIMEK J, HÖHNE E: In-situ Fluorid Aufnahme initialer Kariesläsionen nach Applikation zweier Kinderzahnpasten. *Oralprophylaxe* 12: 65–71 (1990)
- ISSA A I, TOUMBA K J: Oral fluoride retention in saliva following toothbrushing with and without water rinsing. *Caries Res* 38(1): 9–15 (2004)
- KILIAN M, THYLSTRUP A, FEJERSKOV O: Predominant plaque flora of Tanzanian children exposed to high and low water fluoride concentrations. *Caries Res* 13: 330–343 (1979)
- KLIMEK J, GANSS C, SCHWAN P, SCHMIDT R: Fluorid Aufnahme im Zahnschmelz nach Anwendung von NaF- und AmF-Zahnpasten. *Oralprophylaxe* 20: 192–196 (1998)
- LARSEN M J, JENSEN S J: Experiments on the initiation of calcium fluoride formation with reference to the solubility or dental enamel and brushite. *Arch Oral Biol* 39(1): 7–23 (1994)
- LARSEN M J, RICHARDS A: The influence of saliva on the formation of calcium fluoride-like material on human dental enamel. *Caries Res* 35: 57–60 (2001)
- LI Y H, BOWDEN G H: The effect of environmental pH and fluoride from substratum on the development of biofilms of selected oral bacteria. *J Dent Res* 73: 1615–1626 (1994)
- LIMA T J, RIBEIRO C C, TENUTA L M, CURY J A: Low-fluoride dentifrice and caries lesion control in children with different caries experience. A randomized clinical trial. *Caries Res* 42: 46–50 (2007)
- LUSSI A: Kariostatische Wirkungsmechanismen der Fluoride. In: Lussi A, Schaffner M (Hrsg.): Fortschritte der Zahnerhaltung. Quintessenz Verlag, Berlin, pp 25–32 (2010)
- MACHULSKIENE V, RICHARDS A, NYVAD B, BÆLUM V: Prospective study of the effect of post-brushing rinsing behavior on dental caries. *Caries Res* 36: 301–307 (2002)
- MARINHO V C, HIGGINS J P, LOGAN S, SHEIHAM A: Fluoride gels for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev*: CD002280 (2002a)
- MARINHO V C, HIGGINS J P, LOGAN S, SHEIHAM A: Fluoride varnishes for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev*: CD002279 (2002b)
- MARINHO V C, HIGGINS J P, SHEIHAM A, LOGAN S: Fluoride toothpastes for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev*: CD002278 (2003a)
- MARINHO V C, HIGGINS J P, LOGAN S, SHEIHAM A: Fluoride mouthrinses for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev*: CD002284 (2003b)
- MARINHO V C, HIGGINS J P, LOGAN S, SHEIHAM A: Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev*: CD002782 (2003c)
- MARINHO V C, HIGGINS J P, SHEIHAM A, LOGAN S: One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus another for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev*: CD002780 (2004a)
- MARINHO V C, HIGGINS J P, SHEIHAM A, LOGAN S: Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev*: CD002781 (2004b)
- MOBERG SKÖLD U, BIRKHED D, BORG E, PETERSSON L G: Approximal caries development in adolescents with low to moderate caries risk after different 3-year school-based supervised fluoride mouth rinsing programmes. *Caries Res* 39: 529–535 (2005)
- OGAARD B, RÖLLA G, RUBEN J, DIJKMAN T, ARENDTS J: Microradiographic study of demineralization of shark enamel in a human caries model. *Scand J Dent Res* 96: 209–211 (1988)
- OGAARD B, ALM A A, LARSSON E, ADOLFSSON U: A prospective, randomized clinical study on the effects of an amine fluoride/stannous fluoride toothpaste/mouthrinse on plaque, gingivitis and initial caries lesion development in orthodontic patients. *Eur J Orthod* 28: 8–12 (2006)
- O'MULLANE D M: The changing patterns of dental caries in Irish schoolchildren between 1961 and 1981. *J Dent Res* 90 (Spec Iss): 1317–1320 (1997)
- PETZOLD M: The influence of different fluoride compounds and treatment conditions on dental enamel: A descriptive in vitro study of the CaF<sub>2</sub> precipitation and microstructure. In: *Caries Res* 35(1): 45–51 (2001)
- RÖLLA G, SAXEGAARD E: Critical evaluation of composition and use of topical fluorides with special emphasis on the role of calcium fluoride in caries inhibition. *J Dent Res* 69 (Spec Iss): 780–785 (1990)
- RÖLLA G, ÖGAARD B, CRUZ R: Topical application of fluorides on teeth. New concepts of mechanisms of interaction. *J Clin Periodontol* 20: 105–108 (1993)
- RÖLLA G, EKSTRAND J: Fluoride in oral fluids and dental plaque. In: Fejerskov O, Ekstrand J, Burt B A (Hrsg.): Fluoride in dentistry. Munksgaard, Copenhagen, pp 215–229 (1996)
- ROZIER R G, ADAIR S, GRAHAM F, IAFOLLA G T, KINGMAN A, KOHN W, KRÖL D, LEVY S, POLLOCK H, WHITFORD G, STROCK S, FRANTSVE-HAWLEY J, ARAVAMUDHAN K, MEYER D M: Evidence-based clinical recommendations on the prescription of dietary fluoride supplements for caries prevention: A report of the American Dental Association Council on Scientific Affairs. *J Am Dent Assoc* 141: 1480–1489 (2010)
- SAXEGAARD E, RÖLLA G: Fluoride acquisition on and in human enamel during topical application in vitro. *Scand J Dent Res* 96: 523–535 (1988)
- SAXEGAARD E, RÖLLA G: Kinetics of acquisition and loss of calcium fluoride by enamel in vivo. *Caries Res* 23: 406–411 (1989)
- SIÖGREN K, BIRKHED D: Factors related to fluoride retention after tooth-brushing and possible connection to caries activity. *Caries Res* 27: 474–477 (1993)
- STEINER M, MENGHINI G, MARTHALER TH, IMFELD T: Kariesverlauf über 45 Jahre bei Zürcher Schülern. *Schweiz Monatsschr Zahnmed* 120: 1095–1104 (2010)
- STOOKEY G K, MAU M S, ISAARS R L, GONZALEZ-GURBOLINI C, BARTIZEK R D, BIESBROCK A R: The relative anticaries effectiveness of three fluoride-containing dentifrices in Puerto Rico. *Caries Res* 38: 542–550 (2004)
- SUTTON S V, BENDER G R, MARQUIS R E: Fluoride inhibition of proton-translocating ATPase of oral bacteria. *Infect Immun* 55: 2597–2603 (1987)
- TEN CATE J M, DUJSTERS P P E: Influence of fluoride in solution on tooth demineralization. I. Chemical data. *Caries Res* 17: 193–199 (1983)
- TEN CATE J M, VON LOVEREN C: Fluoride mechanism. *Dent Clin North Am*, 43: 713–742 (1999)
- TENUTA L M A, CERZETTI R V, DEL BEL CURY A A, TABCHOURY C P M, CURY J A: Fluoride Release from CaF<sub>2</sub> and Enamel Demineralization. *J Dent Res* 87: 1032–1036 (2008)
- VAN DER MEI H C, ENGELS E, DE VRIES J, BUSSCHER H J: Effects of amine fluoride on biofilm growth and salivary pellicles. *Caries Res* 42, 19–27 (2008)
- WALSH T, WORTHINGTON H V, GLENNY A M, APPELBE P, MARINHO V C, SHI X: Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev*: CD007868 (2010)
- WEATHERELL J A, DEUTSCH D, ROBINSON C, HALLSWORTH A S: Assimilation of fluoride by enamel throughout the life of the tooth. *Caries Res* 11 (suppl 1): 85–115 (1977)
- YENGOPAL V, CHIKTE U M, MICKENAUTSCH S, OLIVEIRA L B, BHAYAT A: Salt fluoridation: A meta-analysis of its efficacy for caries prevention. *SADJ* 65 sutton: 60–64, 66–67 (2010)