Current concepts on the theories of the mechanism of action of fluoride

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The caries-preventive effect of fluoride is mainly attributed to the effects on demineralization/remineralization at the tooth–oral fluids interface. Sub ppm levels of fluoride in saliva are effective in shifting the balance from demineralization, leading to caries, to remineralization. This is attributed to the fluoride-enhanced precipitation of calcium phosphates, and the formation of fluorhydroxyapatite in the dental tissues. Low fluoride levels are found in saliva after toothbrushing with fluoride containing dentifrices. Similar concentrations are ineffective in interfering with processes of growth and metabolism of bacteria, and also do not result in a significantly reduced dissolution of tooth mineral as a result of (firmly bound) fluoride incorporation. Comparative studies of fluoride efficacy have shown that higher concentrations in solution are needed in pH-cycling studies of dentine than in enamel to maintain the mineral balance or to induce remineralization. This is attributed to the greater solubility of the dentine and the smaller size of the dentine crystallites compared to enamel. Fluoride slow-release devices, in the form of fluoride-releasing restorative materials, may serve to increase the fluoride levels in saliva and plaque to levels at which caries can be prevented, also in high-risk patients. Research questions for the next millennium and future perspectives for fluoride applications should be found in the retention and slow release of fluoride after various combinations of fluoride treatment, the combination of fluoride and anti-microbial treatment, the individualization of caries prevention, and the combination of preventive schemes with new developments in caries diagnosis. □ *Caries; demineralization; fluoride; retention*

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The rationale for the caries preventive effect of fluoride has been known for many decades. The fact that fluoride can be incorporated into the crystalline lattice of the mineral of the dental hard tissues, resulting in a tissue less soluble in acid environment, has been the scientific cornerstone for caries prevention. Not only is the reduction in solubility of the mineral hydroxyapatite after fluoride incorporation important, of equal relevance is that a mineral with a lower solubility will precipitate at a higher rate when in contact with a solution containing calcium and phosphate. This explains the effects of fluoride in the mineral of enamel and dentine on both dissolution during caries-like demineralization and precipitation during demineralization. The relevant chemical reactions are schematized in Fig. 1. The fate of a mineral in contact with a solution containing its common ions is depicted in Fig. 2. For the situation of dental enamel this pertains to the minerals hydroxyapatite, fluorapatite, and the common ions, i.e. ions forming part of the mineral-calcium and phosphate.

Effect of fluoride on demineralization

Of special interest is the pH region, where hydroxyapatite is undersaturated and fluorapatite is supersaturated. These values coincide with the pH of dental plaque when the bacteria in plaque are fermenting carbohydrates. In this region, hydroxyxapatite may dissolve while fluorapatite can precipitate. As early as the 1970s Larsen (1) pointed to the fact that in this pH range a subsurface lesion may be formed, a phenomenon that could be attributed to this combination of factors. If the conditions of the demineralizing solution were such that also fluorapatite was undersaturated, then an erosive defect was formed rather than a subsurface lesion. The degree of undersaturation to hydroxyapatite and fluorapatite in determining the condition of the caries defect was studied in great detail in the 1970s and 1980s and led to the consensus agreeing with the original findings of Larsen. Ten Cate and Duijsters (2, 3) studied demineralization in the pH range of 4 to 5 and the fluoride concentration range between 0 and 5 ppm concluding that the demineralization was a function of both pH and fluoride concentration and that, in terms of caries prevention, when a reduction of demineralization was to be achieved this could be done by influencing either or both. A very practical application of this finding was the development of a chewing gum containing bicarbonate and fluoride, the use of which would lead to both an elevation of pH and the increase of fluoride.

The question can be raised whether fluoride could be equally effective at the pH values where erosion takes place. Erosion is the result of the contact between the dental tissues and a solution low in pH, either after the consumption of extrinsic acidic fluids—soft drinks, acidic

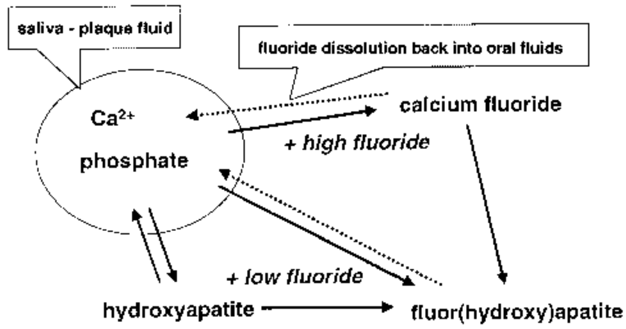

Fig. 1. Some chemical reactions relevant to the caries process involving fluoride.

foods—or when gastric fluids come into the oral cavity (4). Typically this is in the pH range between 1 and 3. As can be inferred from Fig. 2, in this region the saturation conditions are very different from those for dental caries, in that the solutions are not only undersaturated with respect to hydroxyapatite but also with respect to fluorapatite. This implies that introducing fluoride to the system could not lead to a condition where fluorapatite can be formed while hydroxyapatite is dissolving. In spite of this conclusion from a theoretical approach about a possible effect of fluoride on erosion, some authors (5) have reported an effect of fluoride in preventing dental erosion. Nevertheless, a possible application of introducing fluoride to for example soft drinks, at a level where some erosion-inhibiting effect could be expected, would never be feasible from a toxicological point of view. Recently, a calcium-containing beverage has been introduced with a quoted reduced erosive potential (6).

Effect of fluoride on remineralization

Not only has enamel and dentine demineralization been the subject of extensive studies in recent decades, investigators have also focused on the effects of fluoride on enamel and dentine demineralization (7–10). The combined observations show that even in the sub-ppm range fluoride has a substantial and significant effect on the rate of demineralization of dental enamel and dentine. The effects of fluoride on demineralization and remineralization are amplified when they are studied under so-called pH-cycling (11), conditions where enamel or dentine specimens are subjected to the pH changes as they occur in the oral cavity. These occur when individuals have plaque and consume sugars at regular intervals, with interspersed periods of physiological pH and remineralization. The effects of sub ppm fluoride concentrations could even been shown when enamel specimens were subjected to demineralizating and remineralizing solutions with fluoride concentrations as low as 0.02 to 0.06 ppm (12). Similar findings have been made for dentine (13), when it was also demonstrated that dentine has a much higher uptake capacity for fluoride and that higher fluoride concentrations are needed to reach the same effect in inhibiting demineralization and enhancing remineralization (Fig. 3).

Enamel remineralization is a phenomenon that has been known since the beginning of this century, as were the effects of fluoride on it. However, not until the 1960s did remineralization become a process accepted and

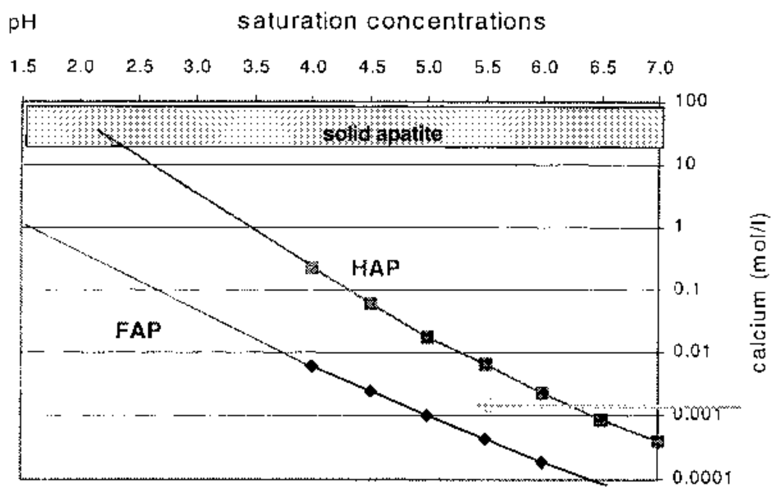

Fig. 2. Solubility isotherms expressing the relationship between the mineral ions (given as calcium ions) and pH at saturation for hydroxyapatite and fluorapatite. The arrow marks the concentration of calcium ions in the oral fluids. The area marked "solid apatite" corresponds with the calcium "concentration" range for solid apatite. This shows that in the low pH range dissolution inhibition by adding calcium (or phosphate) to the acid solution, such as to prevent erosion, is not feasible.

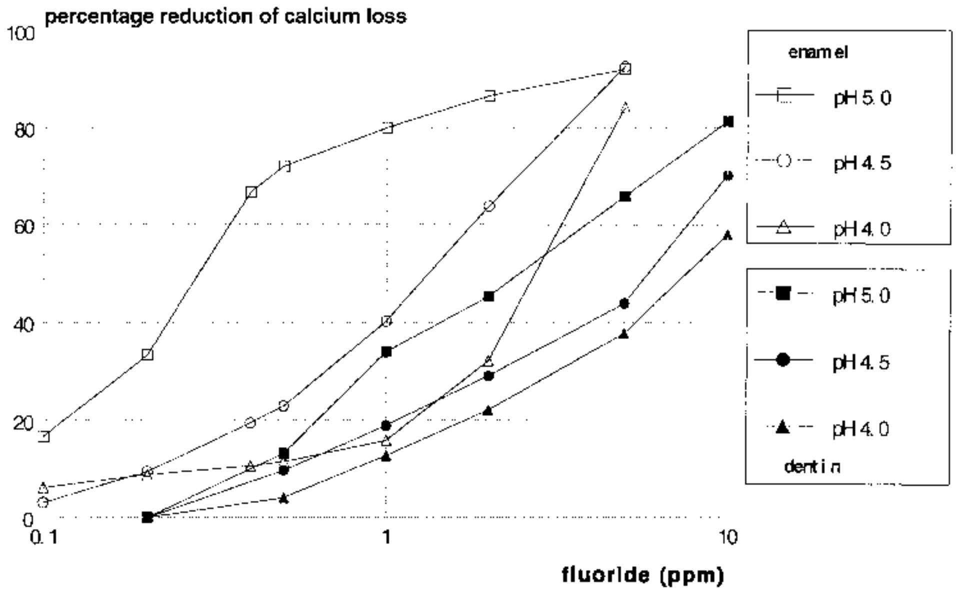

Fig. 3. Reduction of calcium loss for demineralizing solutions varying in pH and fluoride content. Adapted from references 2 and 12. The data show that in the sub ppm fluoride range substantial reductions in calcium (mineral) loss can be found when enamel is demineralized at pH 5.0 or even at pH 4.5. For dentine, considerably higher concentrations of fluoride are required to obtain a similar inhibiting effect.

widely studied by the dental research community. This can be attributed mainly to the studies of Koulourides, who performed many laboratory and intraoral studies (14), and Backer Dirks, Groeneveld and colleagues (15, 16), who demonstrated remineralization in a clinical study. For the community of dental practitioners, enamel remineralization, the natural repair of incipient lesions and the consequences this has for caries diagnosis and treatment planning, did not become common knowledge until the 1990s. Even today the viewpoint that a ‘tooth restored is a tooth lost forever’ is certainly not generally accepted. While demineralization has been the subject of many laboratory and in situ investigations—in this category one refers to studies performed with enamel or dentine specimens placed in appliances put in the oral cavity—for many years, only relatively recently have there been more reports of remineralization observations from clinical studies. Biesbrock et al. (17) re-evaluated the clinical study of Zacherl et al. (18) and concluded that during the 3-year intervention study remineralization was seen on more than 1 tooth per subject in all of 3 groups that used a placebo, a sodium fluoride and a stannous fluoride paste, respectively. Some of the reversals seen during the 1st year of the study re-reversed into a state of caries. This phenomenon was more pronounced in the placebo than in the 2 fluoride groups. Caries reversals are now a phenomenon studied in all clinical trials. To a large extent this has been made possible by the changing views in caries diagnosis. At the time of the peak of the caries epidemic, caries was abundantly present in almost all individuals and progressing at a fast rate. Currently, caries progresses very slowly in most individuals (19). This has initiated research to develop techniques for studying the early stages of caries quantitatively. Rather than discriminating between caries at the cavitation level, as done by the so-called Radike (20) method, the very early phase of mineral loss is detected (21, 22). This has confirmed that remineralization, at least until the stage of arrested lesion is accelerated by fluoride.

Effect of fluoride on oral bacteria

Fluoride has been shown to interact with many metabolic and growth processes in bacteria. Although there is no doubt regarding the various fluoride effects, the current view is that this all occurs at fluoride levels far exceeding those prevailing in the oral cavity. For this reason it has been stated that irrespective of the in vitro data on effects of fluoride on bacteria and dental plaque, the effects of fluoride on the hard tissue demineraliztion and remineralization, which occur even in the sub ppm level, are more important from a clinical point of view (23).

Fluoride levels in the oral fluids

An interesting question in recent years has been how the fluoride in saliva and dental plaque could be raised. After toothpaste brushing, or other method of fluoride supply, the fluoride concentration decreased rapidly following a bi-phasic, exponential pattern. Even when fluoride is applied in the hundreds of ppm concentration range, the

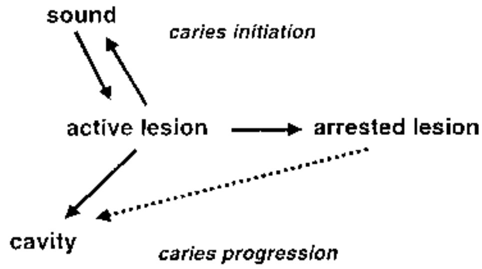

Fig. 4. Schematic representation of the caries process. Fluoride has been shown to have a greater inhibiting effect on caries progression than on caries initiation. Fluoride may also induce lesion arrestment, as evidenced in a clinical trial by the higher number of arrested lesions when subjects receive fluoride treatments (See Fig. 5).

level drops below 1 ppm in 10 min and below 0.1 ppm in 30 min (24). Increased fluoride retention, either accidental—when individuals do not rinse their mouth thoroughly after brushing (25)—or when this is done deliberately in a controlled clinical study (26) leads to lower caries increments (27). Slow release of fluoride from a restorative material or a specially designed slow-release device (28) has been shown to induce remineralization and hypermineralization of dentine (29) and a reduction of caries in a caries-prone population (28).

Future perspectives of fluoride utilization

Future perspectives of fluoride utilization could be found in optimizing the retention and/or slow release of fluoride in the oral environment. The levels needed to significantly reduce caries—or, at a mechanistic level to shift the balance from caries initiation and progression to caries reversal—are apparently in the sub ppm range (see Figs 4 and 5). Some of these investigations should also be looking into the relative efficacy of various types of fluoride treatment in addition to the now commonly used sodium fluoride dentifrices. Although it would seem that twice-daily toothbrushing should be enough to provide the daily amount of fluoride needed to increase the stationary levels found in plaque and saliva, recent studies have demonstrated additional benefits from rinsing in a population using fluoridated toothpastes (27, 30). Mass balance studies carried out during a pH-cycling study show that a small fraction of the toothpaste applied during 'simulated' brushing is retained by white spot lesions and during the pH-cycling converted into fluorapatite. Also with enamel lesions mounted on intraoral appliances it has been shown that fluoride administered is first laid down as calcium fluoride and then converted to fluorapatite during periods of caries challenge (31). In vivo studies of the pharmacokinetics of fluoride, including the multicomponent system of plaque, saliva, mucosal surfaces, but also the hard

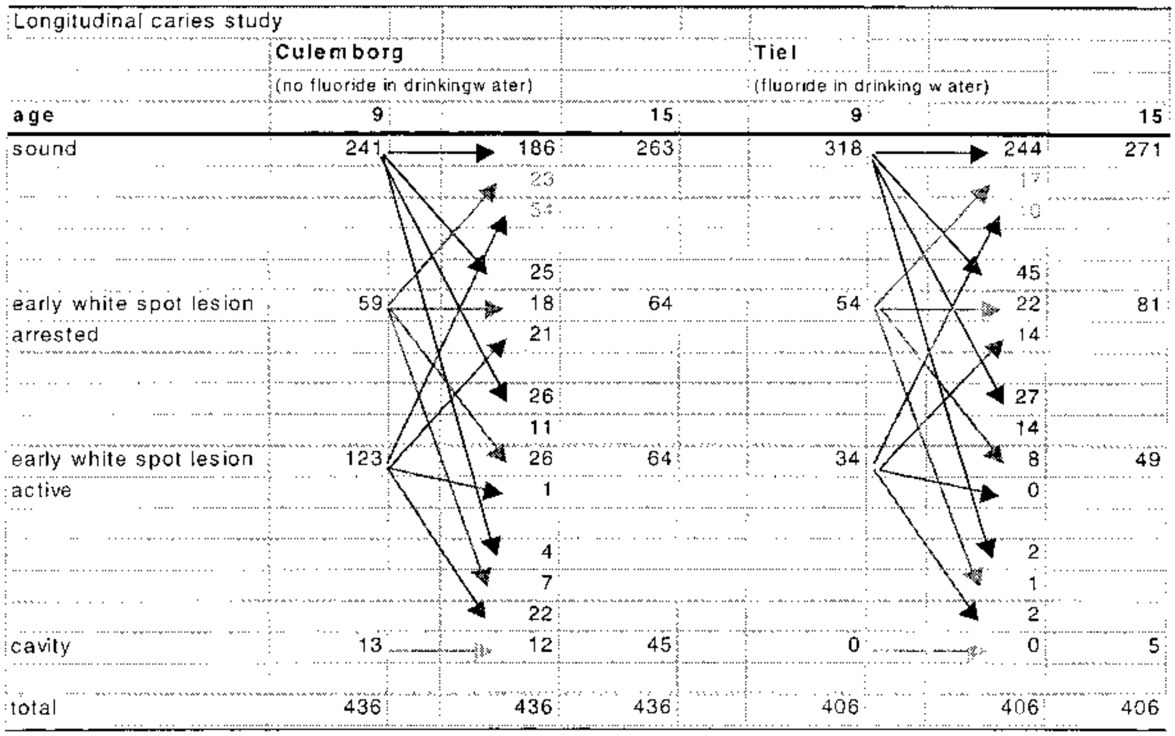

Fig. 5. Data from the Tiel Culemborg study showing the various stages of the caries process and the conversions during the period between 8 and 16 years of age (adapted from references 14 and 15).

tissues, are indicated to optimize fluoride delivery and availability during periods of cariogenic challenge (32).

Recent epidemiological data reveal that caries is still a big problem for a relatively small group in the population ("80% of the caries is found in 20% of the individuals in the younger age groups")—a group that is over-represented by individuals from lower socio-economic classes—and confirm that caries, though an infectious disease that can affect any individual, can be prevented by adequate prevention. Further research should indicate what additional characteristics at the individual level explain increased caries susceptibility, and how this can be prevented. The current perspectives and applications for fluoride are based on the concepts developed during recent decades and might serve to eventually eradicate caries.

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