Overview about fluoride

Fluoride is the ionic form of an element fluorine, a halogen and the most electronegative. Fluorine is the 13th most abundant element in the crust of the earth, and has been found in virtually all inanimate and living things.

Fluoride can reversibly combine with hydrogen ions to form hydrogen fluoride or hydrofluoric acid. Much of the physiological behavior of fluoride can be explained in terms of the diffusibility of HF, which dominates when pH is lower than pKa (3.4).

Fluoride is a potent inhibitor of many enzymes, for example, in the glycolytic pathway.

The elimination of fluoride from the body by the kidneys is many times greater than that of other halogens. Fluoride is an avid calcified tissue seeker and its ability to inhibit and reverse the formation of dental caries is unique.

Fluoride is highly regarded as the cornerstone of modern preventive dentistry. The remarkable decline in dental caries is largely attributed to the proper use of ingested and topical form of fluoride. Various fluoride compounds are added to products such as dentrifices, mouthrinses, topical gels.

The Centers for Disease Control and Prevention have named water fluoridation as one of the 10 most important public health achievements of the 20th century.

We should be aware that fluoride is a hazardous substance when large doses are taken acutely or when lower doses are taken chronically. The effects range from dental fluorosis, reversible gastric disturbances, to skeletal fluorosis and death.
The substance was later identified as fluoride, which occurred naturally in water supplies. And the mottled enamel is now known as dental fluorosis. Regular consumption of drinking water with fluoride was associated with reduction of dental caries.

Later work, primarily by Dean et al., found various levels of fluoride in most water supplies, and water fluoride level of near 1 ppm produced that best balance of caries prevention and low prevalence of dental fluorosis.

Dental fluorosis or mottled enamel is a hypomineralization of enamel that results from excessive fluoride exposure, usually from ingestion, during tooth development. The appearance of fluorosis varies from barely detectable white flecks (common) to severe brown staining with pitting (rare). Mild fluorosis is a minor cosmetic defect, severe fluorosis can increase caries risk because of pitting and loss of the outer enamel.

Overintake of fluoride from birth to 6 years old causes dental fluorosis. The prevalence on primary teeth is less than permanent teeth because most of them develop prenatally. The level of fluoride intake between 15-30 months is the most critical for the development of fluorosis of maxillary central incisors, the most esthetically important teeth.
**Why are we concerned about dental fluorosis?**

- Optimal water F level (~ 1 ppm)
  - 20% prevalence of very mild or mild fluorosis
- Dentistry: Mild fluorosis is an acceptable tradeoff for caries prevention
- Esthetic: ‘mild’ cosmetic defect?
  - No fluorosis: 27% dissatisfied with their tooth color
  - Mild fluorosis: 50% dissatisfied

Why are we concerned about dental fluorosis? Because the prevalence of fluorosis is increasing.

The optimal level of 1 ppmF in water is accompanied by very mild or mild fluorosis with about 20% prevalence. Dental profession believe that mild fluorosis is an acceptable tradeoff for caries prevention. However, when esthetics is becoming more important, this ‘mild’ cosmetic defect is gaining interest.

27% of people without fluorosis were dissatisfied with their tooth color. 50% with mild fluorosis were dissatisfied with the color of their teeth.

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**Water Fluoridation**

1945
Grand Rapids
Michigan

1948: Grand Rapids had 60% less DMFT than Muskegon ‘control’ city

EPA (Environmental Protection Agency)

Max. Contaminant Level (Primary Drinking Water Standards) = 4 ppm F
Naturally existed F in some municipal water & wells: 4-8 ppm F or higher

Water sources with adjusted fluoride concentrations have fluoride levels between 0.7 and 1.2 ppm depending on the area temperature. Water systems in cold climate needs to have higher fluoride level, because people presumably consume less water.

EPA (Environmental Protection Agency) Maximum Contaminant Level under the Primary Drinking Water Standards for fluoride is 4 ppm. Some municipal water sources with naturally occurring fluoride may have up to 4 ppm F, some private wells may have up to 8 ppm F or higher.

Data from the CDC in 2002 reported that about 67% of the US population on public water system (170 million) receives fluoridated tap water. Water fluoridation is the most cost-effective community-based approach to dental caries prevention in the US. Data from 2005 showed that direct annual cost of fluoridation ranges from $0.68-3 per person per year. In most communities, $1 invested in water fluoridation saves $38 or more in treatment costs.

The availability of fluoridated water has produced a halo effect, whereby persons not residing in fluoridated communities receive some of the benefits of fluoridation from consuming products manufactured with fluoridated water.
How does fluoride work?

It was believed that the cariostatic effect of fluoride was due to its systemic incorporation into enamel during development, resulted in ‘more perfect’ enamel crystals that were less acid soluble. The higher concentration of fluoride incorporated, the better the cariostatic effect.

Is that true?  Shark enamel which consists of 100% fluoroapatite can develop caries lesion.

Current philosophy: The caries-reducing effect of fluoride is primarily achieved by its presence during active caries development at the plaque/enamel interface where it directly alters the dynamics of mineral dissolution and reprecipitation, and to some extent, affects plaque bacteria.

Anticaries mechanisms of fluoride: change tooth morphology, effect on plaque bacteria, and inhibit demineralization and enhance remineralization.

The effect of fluoride on tooth morphology is controversial and not universally accepted. The effect on plaque bacteria is debatable. The concentration of fluoride needed for antimicrobial effects is much higher than the concentration needed to affect the demineralization and remineralization process.

Why do we need to know what the mechanisms are?  Because we should maximize the benefit of fluoride and minimize the adverse effects. Like most things in life, more is not necessarily better.

Effect of fluoride on plaque bacteria

As early as 1940, it was shown that fluoride inhibited carbohydrate metabolism in pure culture of streptococci and lactobacilli.  Since then, there are many publications about the effects of fluoride on oral bacteria and dental plaque ecology.  Most of these effects imply a reduced risk of caries.
The major effects of fluoride on dental plaque are:
1. Inhibit bacterial adsorption
2. Reduce proportion of cariogenic bacteria in dental plaque
3. Decrease acid production of dental plaque

The first step in plaque formation is the adsorption of salivary glycoprotein and bacteria to the tooth surface. In vitro experiment showed that 9500 ppm F in solution is needed to inhibit the adsorption of bacteria.

In humans, reduction in plaque deposit was found after the use of mouth rinses and toothpaste with stannous or amine fluoride. But it is questionable if the effect came from the antimicrobial action of the cations (stannous or amine) or fluoride.

After adherence, competition between bacteria will determine the final composition of dental plaque. In a chemostat experiment, where several bacteria grow together, 19 ppmF could prevent mutans streptococci from growing to a larger proportion. It seems like fluoride has selective effect on cariogenic bacteria. However, in vivo this effect could only be seen with high concentration of fluoride.

Proportion of MS in occlusal plaque was reduced after daily application of APF gel (12,300 ppm). In rats, reduced number of MS was found when the drinking water had 250 ppmF, while no difference in plaque flora was found in subjects living in area upto 21 ppmF in drinking water.

Fluoride reduces the acid production by plaque in vivo. A reduction of 0.1 - 0.2 unit in pH drop after a sucrose challenge was found in plaque from individuals drinking fluoridated water or rinsing daily with 0.2% (~900 ppm) NaF solution. No effect was found after a 0.05 % (~200 ppm) rinse.

**Antimicrobial effect of fluoride**

To have the antimicrobial effect, first fluoride has to enter the cell. When external pH is lower than pKa (3.4), HF is dominated. Fluoride enters the cell as HF, not F\textsuperscript{-}, thus it can accumulate in the cell against the concentration gradient. Because cells normally maintain internal pH near neutral (ApH across the cell membrane), HF dissociates into H\textsuperscript{+} and F\textsuperscript{-}. This lowers the intracellular concentration of HF, and results in a continued diffusion of HF into the cell, which again dissociates.

This leads to the accumulation of H\textsuperscript{+} (cytoplasmic acidification) and the accumulation of fluoride in the cell. Fluorides bind to enzymes enolase and proton-extruding ATPase and inhibit the carbohydrate metabolism of bacteria.
**How much fluoride is needed for antimicrobial effect?**

- In vitro: 9500 ppm F in solution inhibit bacterial adsorption to hydroxyapatite
- Reduced MS in plaque after daily use of APF gel (12,300 ppm F)
- Fluoridated water or daily rinse with 0.2% (~900 ppm) NaF solution reduced 0.1 - 0.2 unit in pH drop after a sucrose challenge
- No effect in pH drop after 0.05 % (~200 ppm) NaF rinse
- No reduction of MS in plaque in subjects from area upto 21 ppm F in drinking water

In spite of the evidence for inhibitory effects of fluoride on plaque metabolism, it is not clear to what extent these effects contribute to caries prevention, or how much fluoride is needed. Fluoride concentration needed for antimicrobial effects is much higher than the concentration that patients exposed on a regular basis and surpasses the concentration needed to reduce the solubility of apatite.

**How much fluoride is needed to reduce enamel solubility?**

<table>
<thead>
<tr>
<th>ppm F to reduce solubility</th>
<th>ppm F for antimicrobial effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>At pH 4-5 Fluoride in solution reduces the amount of enamel dissolved</td>
<td>Effective at a few ppm F</td>
</tr>
</tbody>
</table>

As shown in this graph, the presence of fluoride in solution reduces the amount of enamel dissolved at all pH values. Even low concentrations of fluoride, at a few ppm range, are effective. This brings us to the most important cariostatic mechanism of fluoride: effect on the demineralization and remineralization process. (next lecture)

**Fluoride in HAP crystal:**

- Structurally-bound F
  - F- substitute OH-
  - Decrease crystal dimension (F- is smaller)
  - Stabilize the lattice structure
  - Improve the crystallinity
  - Lower dissolution rate

- Strong attraction with calcium (F: the most electronegative)
- F- fill vacancy
- H-bond with O

The most important cariostatic mechanism of F: De- and Remineralization

'Fluorohydroxyapatite' 'Fluoridated hydroxyapatite' 'Fluroapatite-like material'
Fluoride in HAP crystals: Structurally-bound fluoride
To understand the effect of fluoride on de- and remineralization, we have to know how fluoride affects the crystal structure of hydroxyapatite. During mineralization or remineralization, fluoride ions can substitute hydroxyl ions. The atomic size of fluoride ions is smaller, which results in a decrease in dimension in the crystal. In addition, F is the most electronegative of the elements, which results in a strong attraction with calcium. This stabilizes the lattice structure.

Fluoride also improves the crystallinity of enamel apatite by filling in the vacancies in the crystal structure. Fluoride forms a strong hydrogen bond with the oxygen atom in the hydroxyl group. With improved crystallinity and more crystal stability, partially fluoridated hydroxyapatite is less soluble than the pure HAP.

Fluoride incorporated into the crystal lattice of HAP is structurally-bound fluoride. They are called with different names: fluorhydroxyapatite or fluoridated hydroxyapatite or fluorapatite-like material.

Discussion: (group of 6-8)
I believe that the main anticaries effect of fluoride is by changing the equilibrium towards remineralization, not antimicrobial effect.

Why?

How much fluoride is in dental plaque?
- Range from 5-50 ppm wet weight
- 1% is available as fluoride ion
- 15-75% is ionizable
- Some firmly-bound fluoride (bacterial uptake?)
- Plaque matrix concentrate fluoride from saliva:
  +ve charges in matrix & on bacterial surface attract Ca²⁺
  Ca²⁺ bind fluoride.

Fluoride in saliva and dental plaque
Total fluoride in dental plaque ranges from 5-50 ppm wet weight. Of this, 1% is available as fluoride ions, 15-75% is ionizable, and the rest is firmly-bound, possibly uptake by bacteria. The plaque matrix may concentrate fluoride from saliva. Negative charges on the bacterial surface and matrix attract calcium ions which can bind fluoride.

Fluoride concentration in plaque fluid after a 1-min rinse with NaF (0.2%) or MFP (toothpaste slurry; 1000 ppm) rinse was elevated from the baseline value of 0.4 ppm for almost 3 hours. Fluoride level in saliva and plaque decreases exponentially with time after a topical application. According to this, the effect of F should not last longer than an hour after brushing. However, a clinical study showed that F level in saliva and plaque remained increased 18 h afterwards.
This also supports the concept that there is reservoir for F somewhere. One of that is CaF2-like material, and probably the oral mucosa is also a reservoir for F.

### What characters affect caries development?

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Low Caries-Active</th>
<th>High Caries-Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMFT</td>
<td>4.8 ± 5 *</td>
<td>18.9 ± 7.3</td>
</tr>
<tr>
<td>Decayed surface</td>
<td>0 *</td>
<td>3.8 ± 3.1</td>
</tr>
<tr>
<td>Age</td>
<td>26 ± 8</td>
<td>24 ± 8</td>
</tr>
<tr>
<td>Male / female</td>
<td>9 / 14</td>
<td>13 / 11</td>
</tr>
<tr>
<td>Salivary flow (ml/min)</td>
<td>1.5 ± 0.3</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>MS (log CFU/ml saliva)</td>
<td>4.2 ± 1</td>
<td>5.3 ± 1</td>
</tr>
<tr>
<td>Lactobacilli (log CFU/ml saliva)</td>
<td>3.8 ± 0.8</td>
<td>4.5 ± 1.2</td>
</tr>
<tr>
<td>Brushing time (min)</td>
<td>2.8 ± 1.6</td>
<td>2.6 ± 2</td>
</tr>
<tr>
<td>Amount of toothpaste (g)</td>
<td>1.1 ± 0.5</td>
<td>1.2 ± 0.6</td>
</tr>
<tr>
<td>Rinse frequency</td>
<td>1.5 ± 0.7 *</td>
<td>3.6 ± 1.9</td>
</tr>
<tr>
<td>Amount of water to rinse (ml)</td>
<td>70 ± 60 *</td>
<td>190 ± 10</td>
</tr>
<tr>
<td>F in saliva (immediate) (mM)</td>
<td>0.6 ± 0.4 *</td>
<td>0.3 ± 0.3</td>
</tr>
<tr>
<td>F in saliva (accumulate) (mM·min)</td>
<td>6.9 ± 3.9 *</td>
<td>3.9 ± 2.9</td>
</tr>
</tbody>
</table>

*Adapted from Sjögren T, Birkhed D. Caries Res 1993;27:474.*

**Interesting study:**

Rinsing pattern and retention of fluoride affected caries development. Caries risk factors were compared between low and high caries activity groups. There were no differences in salivary flow rate, MS and lactobacilli counts, brushing time and the amount of toothpaste used. But there were significant differences in how many times they rinsed, the amount of water used, the immediate and accumulated amount of F in saliva after brushing.

Can behavior modification affect caries activity?

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**Recommended references**