Fluoride

Fluorine is a natural element present in water, food, soil, and air. However, due to being extremely electronegative, it largely emerges as fluoride (F^-), the monatomic anion of fluorine. Despite being present in only trace amounts in the body (∼2.6 g), fluoride has a significant nutritional and public health impact due to its role in the mineralization of hard tissues including bones and teeth (1).

After ingestion, fluoride is absorbed by passive diffusion from the gastrointestinal tract, with stomach and upper small intestine absorption accounting for 20–25% and 70–75% of total fluoride absorption, respectively (2). Plasma fluoride concentrations increase sharply and reach a peak within 20–60 min after ingestion (2). Almost 99% of body fluoride is incorporated into the apatite lattice of bones and teeth. Unabsorbed fluoride, which is ∼10% of ingested fluoride, is excreted through feces (2). The removal of fluoride occurs almost exclusively from the kidneys. In healthy adults, ∼35% of absorbed fluoride is retained in the body, and in children this is almost 55% (1, 2).

Deficiencies

Although fluoride is not considered an essential nutrient, it has a valuable role in improving oral health. Fluoride has been viewed as the fundamental element for prevention of dental caries. The cariostatic effect of fluoride is mainly due to its ability to inhibit enamel demineralization and promote enamel lesion remineralization. Fluoride also interferes with growth of oral plaque bacteria that cause dental caries (3).

However, excessive chronic fluoride exposure during the period of tooth formation (i.e., the first 6–8 y of life) can cause dental fluorosis, characterized by the presence of white opaque lesions due to increased enamel porosity (1, 2).

Diet Recommendations

Despite well-conducted prospective studies, the optimum level of fluoride exposure that provides the highest degree of protection against caries, with minimum dental fluorosis, is not precisely known. This is mainly because several factors can modify fluoride metabolism, affecting the relation between intake and retention of fluoride and consequently the risk of developing dental fluorosis. Among these factors are genetics, diet composition, nutritional status, physical activity, renal impairment, and acidosis due to acid-base disturbances (2).

Due to insufficient data, no Dietary Reference Value for fluoride is currently available. Nevertheless, the US Institute of Medicine (IOM) has proposed adequate intakes (AIs) based on estimated intakes that seem to lessen occurrence of dental caries while minimizing undesirable health effects (4). The suggested AI for infants from birth to 6 mo is 0.01 mg/day, whereas for children older than 6 mo and adults the AI is estimated as 0.05 mg/kg body weight/day. The IOM has also proposed a daily fluoride intake of 0.1 mg/kg body weight as the upper limit of fluoride for infants and children up to 8 y old (4).

Food Sources

The key sources of systemic fluoride intake are the diet and inadvertent ingestion of dental care products containing fluoride (3). In children, the amount of fluoride ingested during toothbrushing could vary from 0.13 to 0.59 mg, depending on their age, the quantity of toothpaste used, and their rinsing behaviors (3). In children <6 y of age, $\leq 87\%$ of total daily fluoride intake is due to unintentional ingestion of toothpaste (1, 3). On the other hand, diet is the main source of fluoride intake in infants <12 mo old. Dietary sources of fluoride include naturally fluoridated water as well as dietary fluoride supplements (including artificially fluoridated water, milk, and salt) and other foods and drinks prepared with fluoridated water. In countries where tea is largely consumed, it is a significant source of fluoride. Fluoride concentrations in tea leaves range from 26 to 820 mg/kg ,and in tea infusions from 0.29 to 8.85 mg/L (3). Generally, raw fruits and vegetables, meat, and unprocessed foods and beverages contain low concentrations of fluoride (3). However, concentrations of fluoride in mechanically deboned meat as well as seafoods such as fish and shellfish products containing bone and skin could be >10 mg/kg (3).

Clinical Uses

Fluoride has been largely utilized worldwide to control dental caries. The beneficial effect of fluoride arises primarily from the constant presence of low concentrations of fluoride in the fluid phases of the oral environment. Systematic reviews with meta-analysis revealed percentages of reduction in decayed, missed, and filled teeth by optimally fluoridated water, toothpastes, mouth rinses, gels, and varnishes of 26%, 23%, 27%, 28%, and 43%, respectively, compared with no treatment or placebo (2). Importantly, fluoride does not need to be ingested to protect against caries, because the protective effect is essentially "topical" (i.e., when the ion is in contact with the teeth). However, ingested fluoride also exerts its anticaries effect when the ion returns to the oral cavity via crevicular fluid or saliva. Moreover, the pre-eruptive effect of fluoridated drinking water has been recognized, at least for the prevention of caries in the pit and fissure surfaces of permanent molars, as these surfaces are less accessible to "topical" fluoride (2).

Toxicity

The only side-effect attributed to the regular use of optimally fluoridated water (0.7–1.0 mg/L) and conventional fluoridated

Adv Nutr 2022;13:2679–2680; doi: https://doi.org/10.1093/advances/nmac050.

toothpaste (1000–1500 μg/g) is mild dental fluorosis, which is not regarded as a public health problem (2). However, with higher fluoride doses or prolonged chronic exposure, the enamel becomes less mineralized and posteruptive pitting and/or brown stains can occur, which characterizes severe fluorosis. Severe cases of dental fluorosis appear only in endemic areas with high concentrations of fluoride naturally present in the drinking water. It is noteworthy that in endemic areas where water fluoride concentrations are $\geq$5 mg/L, skeletal fluorosis can also occur (2).

Acute toxicity occurs when a large single dose of fluoride (>5 mg/kg body weight) is ingested. Early symptoms of acute toxicity include nausea, vomiting, abdominal pain, diarrhea, weakness, and hypocalcemia (3).

Recent Research

Since the introduction of fluoridation schemes such as fluoridated water, salt, and milk in the late 20th century to lower the incidence of dental caries, its benefits and risks have been frequently discussed and debated. Special focus has recently been given to the effect of fluoride on cognitive neurodevelopment. Several epidemiological studies have proposed that fluoride is a human developmental neurotoxicant that degrades measures of intelligence in children. However, based on the sum of presently available scientific evidence, a recent critical review concluded that fluoride cannot be presumed as a human developmental neurotoxicant at the current concentrations of community water fluoridation of 0.7–1.0 mg/L, as well as naturally occurring exposure circumstances when these do not exceed the AI (5). On the other hand, evidence from animal studies suggests that intake of low doses of fluoride in the drinking water, similar to those found in public water supplies, increases insulin sensitivity and reduces blood glucose (6). The probable mechanism involves reduction in phosphoenolpyruvate carboxykinase, a positive regulator of gluconeogenesis, leading to increased cell glucose uptake. These findings, if confirmed in epidemiological studies, open a new perspective regarding the use of fluoridated water for the prophylaxis of diabetes (6).

The involvement of gene–environment interaction is an important topic when considering the health effects of fluoride. Physical activity is one of the major environmental factors that might alter the pharmacokinetics of fluoride and subsequently affect body fluoride retention. Human studies suggest an increase in the fraction of ingested fluoride absorbed systemically with moderate exercise (7). Additionally, animal studies have shown a significant decrease in fluoride concentration of plasma in rats that exercised, whereas high-intensity training exercise exhibited no effect on plasma fluoride concentration in fluorosis-susceptible mice (8). Moreover, fluoride accumulation in femur has been shown to be increased by exercise in fluorosis-resistant mice whereas femur fluoride concentration in fluorosis-susceptible mice was not affected by exercise (8).

Acknowledgments

The authors' responsibilities were as follows—FVZ and MB: conceived and prepared the article; FVZ: took the lead in writing the manuscript; and both authors: read and approved the final manuscript.

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The authors reported no funding received for this study.

Author disclosures: The authors report no conflicts of interest.

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