Narrative Review:
Efficacy and Safety of Fluoride in Children: A Narrative Review

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ABSTRACT

Context: Fluoride is a necessary element for bone growth and the prevention of dental caries. Diet and dentifrices are the most significant sources of fluoride exposure in children. The concentration of fluoride differs in various types of foods. Although at optimal levels, fluoride has beneficial effects on dental health, in high concentrations, it has some adverse effects, such as structural and functional defects in organs like the kidney and interference with thyroid function. High doses of fluoride can lead to fluoride toxicity, affecting different parts of the body like teeth. Our study aimed to review the previous studies on fluoride toxicity and provide relevant information to dentists and specialists about fluoride safety in children.

Evidence Acquisition: The data we used in our review were found from articles published until 2019 and collected from official web pages and documents published from different international institutions. Topics discussed in this review were dietary intake of fluoride, fluoride metabolism, history of fluoride use, mechanism of fluoride action, overuse, and toxicity of fluoride. After the abstract screening, we reviewed relevant studies for full-text review.

Results: Fluoride is generally found in the human daily diet. There are different sources of fluoride, such as fluoride supplements or fluoride dentifrices. Fluoride also has a topical protective effect against teeth decay. Ingestion of high doses of fluoride in a short time can lead to fluoride poisoning. Emergency treatment is needed when the toxic dose of 15 mg/kg has been exceeded. This problem usually happens in children while using products such as fluoridated toothpaste for oral hygiene; this illness can threaten their overall health.

Conclusions: Fluoride can damage organs such as the liver and kidney as the principal organs susceptible to toxicity induced by fluoride. Although the intake of high doses of fluoride has some adverse health effects, its topical use is considered safe. Fluoride can improve children's dental health in different ways and prevent caries.

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1. Context

Fluorine (F) is the ninth element in the periodic table of elements, a halogen family member that forms approximately 0.08% of the earth's crust. Fluorine is naturally found in soil, water, air, plants, and animals in various amounts (1). Fluoride is the simplest anion of fluorine. From the chemical perspective, fluoride is the most electronegative element because of its small atomic radius and high oxidizing potential, allowing it to bond to all other chemical components (2).

In low concentrations, fluoride has a beneficial effect on longevity and dental health (3). It is one of the basic anions required for bone growth and the prevention of caries (4). But, when humans are exposed to high concentrations of this anion, some adverse effects such as skeletal fluorosis or thyroid function alteration may occur (3).

Many scientific papers have noted the efficacy of fluoride in improving oral health (2). All natural water sources contain fluoride in various concentrations. For instance, according to recent studies, the fluoride concentration in seawater is approximately 1.2-1.5 ppm, while fresh drinking water typically exhibits a concentration ranging from 0.01 to 0.03 ppm (5).

Generally, nutritional sources such as meat, fruit, and vegetables contain very low fluoride levels (6). But except for these sources, tea and rice contain high fluoride doses (about 2 ppm) (7). The concentration of fluoride in black tea is the highest among different types of tea (8). Diet and dentifrices are the most significant sources of fluoride exposure in children (9-14).

In dentistry, there are various topical agents and supplements to prevent dental decay, such as dental varnishes, rinses, drops, gels, and tablets (6).

Dental fluorosis is a developmental defect that occurs in the immature enamel during the crown formation of permanent teeth and is the most common impact of excessive fluoride which appears on tooth surfaces (during the first 6 years of life) (5, 6). Because of the variety of flavors in children's toothpaste, they like to swallow toothpaste and therefore are at a higher risk of developing this complication (15).

Nowadays, fluoride poisoning can occur due to the uncontrolled consumption of dental and oral hygiene products and over-fluoridated water (5). Therefore, it is crucial to control the amount of fluoride intake (16). Studying and understanding the metabolism of fluoride elucidate the influence of fluoride on human health (17).

Our study aimed to review the previous studies on fluoride toxicity and also provide relevant information to dentists and specialists about fluoride safety protocols in children. This article pronounced the beneficial and adverse effects of fluoride on human health.

2. Evidence Acquisition

The data we used in our review were found from articles published until August 2019 and using fluoride, toxicity, and children as keywords, collected from official web pages (Google Scholar, Scopus, Ovid, PubMed, and ScienceDirect) and documents published from different international institutions. The search was restricted to articles published in the English language. Topics discussed in this review are the history of fluoride intake, dietary intake of fluoride, fluoride metabolism, the mechanism of fluoride action and overuse, and toxicity of fluoride. After the abstract screening, the full-text of related studies was reviewed. The following types of studies were excluded from this review: in vitro studies, animal studies, studies published in languages other than English, case reports, narrative reviews, medical record reviews, meeting abstracts, historical articles, editorials, letters, and commentaries. The included studies were the ones in which authors published information about exposure to fluoride in children and reported outcomes of interest (such as caries and fluorosis) in participants over time.

3. Results

Dietary intake of fluoride

Fluoride is generally found in our daily diet regimen. It exists in different concentrations in many foods that are mentioned in Table 1 (5). Various fluoride sources include fluoride supplements, fluoride dentifrices, fluoride in water, and foodstuffs (7, 8).

In a previous study, Cardoso et al. reported that the amount of fluoride intake through dentifrices was higher than that through diet (11). Mizira et al. reported the intake of fluoride via dentifrices as 56.3%, water 17.2%, food 11.8%, and in other beverages, this amount was reported 14.7%. It should be noted that this study was conducted in a region with fluoridated water (12). The concentration of fluoride in toothpaste is approximately 0.1% or 1000 ppm (6).

Table 1. The concentration of fluoride in different types of food (5, 9, 10)

Type of Tood	Concentration of Fluoride (ppm)
Meat	0.2-1
Fish	2-5
Bread	0.39
Dairy products	0.25
Fruits (in general)	0.06
Black tea	3-5
Vegetables	0.1-0.4
Eggs	0.01
Milk (Cow)	1.73-6.87
Oils and fats	0.25

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Several organizations, such as the United States Food and Drug Administration, recommended using a smear of toothpaste (a portion the size of a grain of rice) for children under 2 years old and also a pea-size for children younger than 6 years old (13).

Fluoride metabolism

Approximately 90% of ingested fluoride is absorbed from the Gastrointestinal (GI) tract, and the remainder is excreted in the feces (14). Fluoride is bounded to proteins in the plasma; the peak concentration of fluoride in the blood reaches about 20-60 minutes after consumption (15). The concentration of fluoride in the blood is approximately 1% ppm. Fluoride retention in different organs is around 30% in adults and 50% in children. About 99% of these amounts are present in mineralized tissues (teeth and bones), and the remaining 1% is stored in soft tissues (15). Kidney is the main organ responsible for fluoride excretion. Excretion from other sources (such as saliva and sweat) is negligible (14).

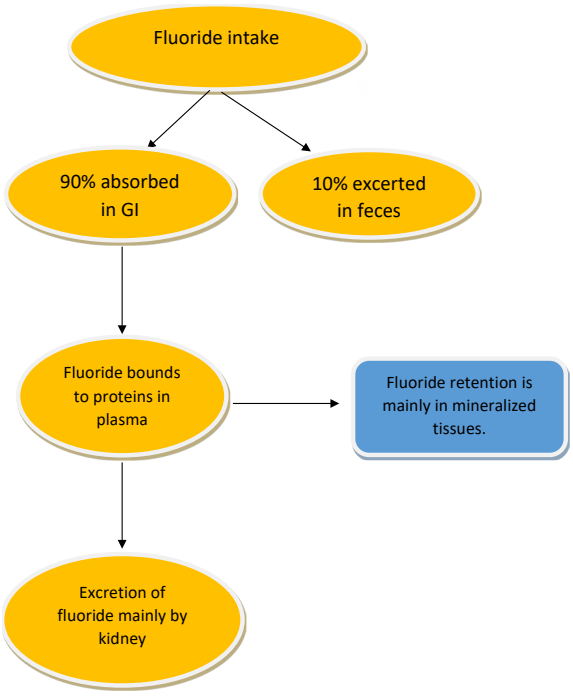

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Figure 1. Summary of metabolism and excretion of fluoride

Generally, various factors can affect fluoride metabolism, such as acid-base disorders, physical activity, diet, genetics, and kidney function (15). When the fluoride concentration is low, it can enter into the placenta from the mother's body (16). If its concentration exceeds 0.4 ppm, the placenta acts as a protective barrier and prevents additional fluoride from penetrating the fetus (16, 17). Fluoride can be transmitted to the mothers' milk, but its concentration is low (18).

The liver is a major site of metabolism in the body; therefore, it is especially prone to fluoride intoxication (19). On the other hand, the kidney is also susceptible to toxicity induced by fluoride as it is the main organ responsible for the excretion of fluoride (20). Figure 1 is a diagram that gives a summary of fluoride metabolism. Several animal epidemiological studies have confirmed that excessive fluoride concentrations could damage the liver and kidneys (21).

Table 2. Fluoride levels in drinking water of different nations (9)

Country	Reported Fluoride Levels in Drinking Water (mg/L) 1 mg/L=1 ppm
China	21.5
Finland	Higher than 3 mg/L
Turkey	At most 13.7
Indonesia	0.1-4.2
Germany	8.8
Pakistan	8-13.52
Spain	2.5-4.59
USA (Texas)	0.3-4.3
Japan	1.4
India	0.5-69.7

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Water fluoridation

Water fluoridation is an effective way to establish good oral health (22). When fluoride is exposed to teeth surfaces, it bonds with hydroxyapatite crystals and increases their resistance against acids; therefore, it reduces the dental caries progression (23). Water fluoridation is an effective remedy for preventing dental caries due to establishing fluorohydroxyapatite crystals and their higher resistance against microorganisms. This method is routinely used in developed countries (24). Water fluoridation should be done under control because excessive fluoride in drinking water can lead to fluorosis (25). In the united states, water fluoridation was introduced in the 1940s at the level of 0.7 to 1.2 ppm (26). According to Table 2, due to the high concentration of fluoride in some regions of countries such as China, Turkey, and Pakistan, a method should remove excessive fluoride from public and individual water supplies (9).

The beneficial effect of fluoride upon dental health

Topical use of fluoride leads to the prevention of dental caries via several mechanisms described below. As we know, hydroxyapatite crystals are the main mineral components in the teeth's enamel (27). When fluoride ions bond to hydroxyapatite, they form fluorohydroxyapatite crystals, which are more resistant to dissolution in acidic conditions that occur in dental caries (28).

$$Ca_{10}(PO4)_6(OH)_2 \xrightarrow{F^-} Ca_{10}(PO4)_6 F_2$$

(hydroxyapatite) (fluorapatite)

According to this formula, fluoride ions replace hydroxyl ions in the hydroxyapatite crystal. Since fluoride ions are much bigger than hydroxyl ions, they increase hydrogen bonding and the density of crystal lattice, therefore, decrease the solubility of the crystals in an acidic environment (29).

The caries preventive effect of fluoride may also occur due to the inhibition of enzymes involved in glycolysis processes such as enolase and proton releasing adenosine triphosphatase (ATPase) (30). Dental caries is the most common chronic diseases in children all around the world. It is proved that fluoride exposure can provide the highest protection against dental caries (31).

Toxicity of fluoride

Fluoride toxicity is classified into chronic and acute toxicity. Excessive ingestion of fluoride in a short time can result in acute toxicity. Nausea, vomiting, abdominal pain, and diarrhea are early symptoms of acute fluoride toxicity that can be followed by shallow breathing, cyanosis, dilated pupils, spasms of extremities, hypotension, respiratory acidosis, and convulsion. Generally, death from high doses of fluoride ingestion can occur within a few hours (32).

According to previous studies, the Probable Toxic Dose (PTD) of fluoride was defined at 5 mg/kg of body weight, as mentioned in Table 3 for different age groups.

Table 3. Probable Toxic Dose (PTD) of fluoride in children of different age groups

Age groups	PTD	Explanation
to 2-year-old children, ~ 10 kg (22 lb)	50 mg F	Swallow 50 g (2 oz) of toothpaste (or ¼ tube) with 1000 ppm fluoride, or 215 mL of 0.05% F-mouth rinse (1.3 bottles), or 50 tablets of 1 mg F-supplement to reach PTD. Some kinds of toothpaste are 'extra-strength' and contain 1500 ppm fluoride. Therefore, the PTD for these high F kinds of toothpaste is only 33 mg (or 1.6 tubes) for a 10-kg child. Some prescription mouth rinses contain 0.2% or 0.4% F, 4 times higher than over-the-counter products.
5-6 years old children, ~ 20 kg (44 lb)	100 mg F	½ tube toothpaste with 1000 ppm F Ingesting 100g (75 mL) of toothpaste which contains 1000-1500 ppm of fluorides or 100 pills that contain fluorides (0.5-1 mg fluoride).

PTD (probable toxic dose)=5 mg/kg.

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PTD is the dose of a substance in the body that higher than this level that can be associated with life-threatening symptoms that may require immediate treatment. Emergency treatment is needed when the PTD of 15 mg/kg has been exceeded (33). Figure 2 demonstrates some emergency treatments that could be used in the case of fluoride overdose.

Dental fluorosis, as a type of chronic fluoride toxicity, is defined as hypo-mineralization of the enamel that can occur during the first few years of life due to excessive exposure to fluoride (6). The severity of this disorder depends on the dose of fluoride, duration of exposure, and age of the individuals (34). Yellowish or brownish striations on teeth, deformity of enamel and dentin, and interference with enamel mineralization are the main clinical manifestations of dental fluorosis (20). In 1934, Dean created an index commonly used for classifying different types of dental fluorosis (35). Table 4 demonstrates the Dean's fluorosis index.

Usually, young children tend to swallow toothpaste and are at a higher risk of developing dental fluorosis because they are typically unable to rinse out toothpaste from their mouths (36). Therefore, the primary source of dental fluorosis remains inside oral hygiene products (37). The severity of dental fluorosis lesions increases when the amount of fluoride in drinking water exceeds from 0.7 ppm (2).

However, the mechanism of chronic fluoride toxicity in the whole body is not yet clearly understood. Some studies reported that oxidative stress is one of the essential mechanisms of toxicity in dental fluorosis. Oxidative stress is defined as the imbalance between the production rate of free radicals and the effects of protective antioxidants in the body (38). Chronic fluorosis can induce the generation of free radicals and also inhibit the enzymatic antioxidant defense system in the body that can lead to cellular damage (39).

Fluoride and alteration on thyroid function

High fluoride concentrations (100-200 ppm) can interfere with normal thyroid function. It can increase Thyroid-Stimulating Hormone (TSH) and decreases the levels of T4 and T3 hormones and consequently leads to hypothyroidism (40) So, in areas which fluoride intake is exceptionally high, the secretion of thyroid hormones can be affected (41). Fluoride interferes with the activity of enzymes that accelerate the conversion of thyroxin into active hormones. According to an experimental study conducted by Rahman and Fetouh, so-

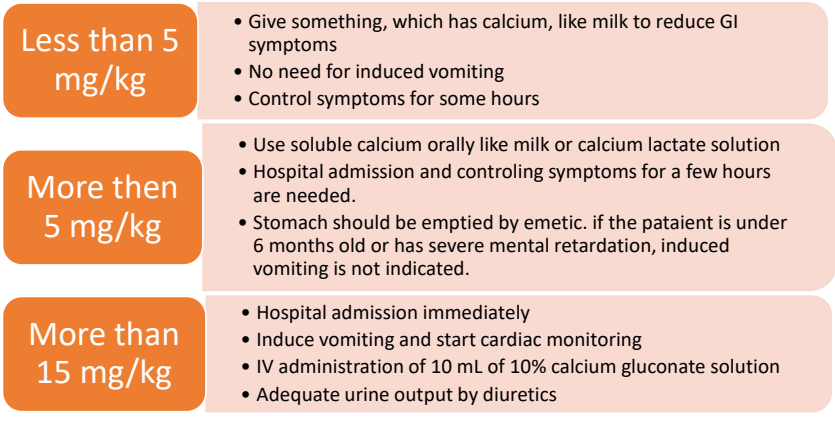

Figure 2. Treatment approaches for fluoride overdose

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Table 4. Classification of dental fluorosis

Diagnosis	Criteria
Normal	Usual translucent semi-vitriform type of structure: smooth, glossy, usually a pale creamy-white color
Questionable	A slight deviation from normal translucency, ranging from a few white "flecks" to occasional white spots
Very mild	Less than 25% of the tooth's surface is affected. Small, opaque, paper-white areas scattered irregularly over the tooth. Tips of cusps often show "snow capping"
Mild	More than 25% but less than 50% of the tooth's surface are affected. More extensive, opaque, paper-white areas
Moderate	All enamel surface is affected, frequently with brown staining.
Severe	All enamel surface is affected, with widespread brown staining and discrete or confluent pitting. Teeth may exhibit a "corroded" appearance.

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dium fluoride exposure led to thyrocytes' structural and functional damage. Therefore the production of thyroid hormones is disturbed (42).

Fluoride effect on neuronal health

Recent studies showed that exposure to a high fluoride concentration has a destructive impact on mental development, such as Intelligence Quotient (IQ) in children (43). For example, in a meta-analysis review study conducted in China, it was observed that children who live in areas where fluorosis is prevalent have 5 times lower IQ compared to those who live in areas where fluorosis is scarce (44). The developmental neurotoxicity associated with fluoride is a significant concern these days (45). Ingesting a high amount of fluoride can cause brain-specific metabolic disorders because fluoride can inhibit several neuronal enzymes (46). The brain damage mechanism is related to different reactions such as increased myelin-associated glycoprotein levels, a decrease in nicotinic receptors, changes in phospholipid content, and some other reactions (47). Vani and Reddy conducted a study on mice to analyze the effects of fluoride on some brain enzymes. They concluded that high doses of fluoride in the hippocampus causes degeneration of neurons and changes in free radical metabolism (48).

Fluoride effect on soft tissue

Excessive fluoride exposure has a destructive impact on different soft tissues, including the lungs, kidney, liver, and heart (20). Many studies have declared that the adverse effects of fluoride on soft tissues might be associated with free radicals and oxidative stress (49). For example, the ingestion of excessive fluoride can elevate liver enzymes levels and decreases plasma antioxidant status (20, 50). Song et al. showed in an in vivo experi-

Table 5. Effects of F^- on human health

Effects		References
Effects on teeth	Dental fluorosis as chronic toxicity of fluoride	Fejerskov & Kidd, 2009 (34)
Effects on thyroid function	Dysfunction in thyroid gland	Sarkar & Pal, 2014 (41)
Effects on soft tissue	Nausea, vomiting, abdominal pain	Kabir et al. 2019 (20)
	Kidney disease and renal dysfunction	Niu et al. 2016 (50)
	Alteration in liver enzymes	Niu et al. 2016 (50)
Effects on neuronal health	Reduction in Intelligent Quotient (IQ) and ability to think	Peckham& Awofeso, 2014 (43)
	Inhibition of neuronal enzymes	Zuo et al. 2018 (46)
	Causing brain-specific neuronal disorders	Zuo et al. 2018 (46)
	Degeneration of neurons	Vani & Reddy, 2000 (48)
Developmental effects	Closed spina bifidia, sudden infant death, Down's syndrome	Doull et al. 2006 (52)

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ment that ingestion of high sodium fluoride levels stimulates apoptosis pathways and DNA damage in rats (51).

Developmental effects of fluoride

There are three types of developmental disorders caused by excessive fluoride intake: Closed spina bifida, sudden infant death, Down's syndrome (52). Some studies show that excessive fluoride intake has adverse developmental effects in animals, but human studies are inconclusive (20). Table 5 gives a summary of the effects of fluoride mentioned in this article.

4. Conclusion

Fluoride is present in our daily lives. We are exposed to fluoride through different sources such as fluoride supplements. Fluoride is beneficial for our dental health and bone growth, but it can be toxic in high concentrations and cause various problems such as dental fluorosis. Brown stains, deformity of enamel and dentin, and change in the color of teeth can be signs of dental fluorosis and is essential to notice. Also, if the fluoride concentration is between 100-200 ppm, it can interfere with normal thyroid function. Although using high doses of fluoride has adverse effects, it can improve children's dental health in several ways, especially preventing caries.

Ethical Considerations

Compliance with ethical guidelines

This was a review study and did not require ethical considerations.

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Authors' contributions

Conceptualization: Azam Nahvi, Pegah Nasiri; Methodology: Milad Arab-nozari; Investigation: Pegah Nasiri, Nadia Elyassi Gorgi; Writing – original draft: All authors; Writing – review & editing: Ali Malekzadeh Shafaroudi; Supervision: Azam Nahvi, Ali Malekzadeh Shafaroudi.

Conflicts of interest

The authors declared no conflict of interest.

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