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Original article

Anterior Teeth Fluorosis: Insights and Concepts about Prevalence, Pathogenesis, Diagnosis, and Prevention

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Dental fluorosis is a developmental disturbance of enamel caused by excessive fluoride intake during tooth formation, particularly between the ages of 20 to 36 months. This condition manifests primarily as aesthetic alterations, especially in anterior teeth, ranging from mild white striations to severe brown stains and enamel pitting. Fluoride, found naturally in water and various food sources, becomes harmful when ingested in excess, particularly in regions with high natural fluoride levels, such as parts of Pakistan. The severity of dental fluorosis depends on several factors, including fluoride concentration, duration of exposure, nutritional status, and genetic predisposition. The pathophysiology involves disrupted ameloblast function and altered calcium signaling, often resulting in porous, hypo-mineralized enamel. Despite fluoride's well-documented benefits in caries prevention, its excessive intake has been epidemiologically linked to increased fluorosis prevalence. Accurate diagnosis involves clinical examination and consideration of systemic fluoride history. Preventive strategies include controlling fluoride exposure in early childhood, particularly through safe water consumption and appropriate use of fluoridated products. Current treatment is largely aesthetic, involving procedures like micro-abrasion and bleaching. Future research is needed to further understand the molecular mechanisms of fluorosis and explore novel prevention and therapeutic approaches.

Introduction

Dental fluorosis is characterized by a disruption in the development of tooth enamel deterioration; this is brought on by too much quantity of fluoride exposure throughout growth, which leads to enamel that contains fewer minerals and in- wrinkled porosity. The seventeenth most prevalent element in the crust of the earth, fluorine, is a gas that never exists in nature in a free state. It only occurs as fluoride compounds, which are components of minerals found in rocks and soil, when combined with other elements. In plasma, fluoride can be found in both ionic and bound forms, with the bound form being more prevalent. The levels of fluoride in human saliva, which range from 0.01 to 0.05 ppm, are marginally lower than those in plasma. One of the most significant developments in stomatology was the identification of fluorides' anticariogenic qualities, which promoted the creation of practical strategies for preventing and managing dental caries. However, when fluoride intake exceeds acceptable levels, there is a chance of getting dental fluorosis [1]. A person's weight, degree of physical activity, nutritional status, bone growth, and the timing and duration of their overexposure to fluoride all influence the severity of dental fluorosis, indicating that varying fluoride dosages may result in varying degrees of dental fluorosis. The most concerning aspect of dental fluorosis is the aesthetic alterations in permanent dentition, which are more likely to develop in children who get excessive systemic and topical fluoride exposure between the ages of 20 and 30 months. A daily fluoride intake of 0.05 to 0.07 mg F/kg is considered safe [2].

Several studies have found that fluorinated toothpastes, tea, tobacco, and pans all contribute to dental fluorosis symptoms. Since most drinking water in Pakistan comes from subterranean sources, high fluoride levels in the water may have a negative impact on the dental health of those who live in the area. Therefore, current research has been conducted to determine the impact of fluoride-rich water and toothpaste on the prevalence of fluorosis in districts Mianwali and Mardan [3-7].

Pathologically, the etiology of dental fluorosis, a deficiency in enamel growth, may be linked to excessive fluoride ingestion. Although it can manifest at any point during development, it is typically linked to the early stages of life, between 20 and 36 months, and some authors classify it as an endemic condition in regions where water contains amounts greater than 1.5 mg/L [8].

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Exposure to fluoride that is above optimal levels during enamel formation may induce the appearance of dental fluorosis [9, 10, 11]. It has been confirmed that there is a significant positive relationship between fluoride intake by water and the prevalence of dental fluorosis [12-15]. The impact of environmental contamination on body burden is usually based on biomonitoring data on fluoride content in urine and/or blood. Due to its specific informative potential, hair analysis has also been used for exposure assessment [16-19]. Therefore, epidemiologic research supports fluoride's benefits for oral health. Numerous systematic reviews [20-25] attest to fluoridation's cost-effectiveness and clinical efficacy. Fluoridated water consumption lowers tooth decay in adults and children by about 25% [26, 27]. Fluorosis is categorized as mild, moderate, or severe in clinical settings [28-34]. The amount of fluoride in urine and plasma is related to the amount of fluoride in the water that is drunk [32,33].

Pathophysiology of dental fluorosis in anterior teeth

Four sources; fluoridated drinking water, fluoride supplements, topical fluoride (particularly fluoride toothpastes), and child formula—have been found to raise the risk of dental fluorosis by researchers in regions where fluoride is added to drinking water. Additionally, certain kids' industrialized diets may also play a significant role in their daily fluoride intake [35]. In contrast to the etiologic factor of dental fluorosis, which has been thoroughly identified as the chronic exposure to high concentrations of fluoride between the ages of 0 and 5 years, little is known about the cellular and molecular pathways impacted by fluoride and contributing to the development of fluorosis [36].

Excessive fluoride intake during tooth growth is the cause of dental fluorosis. The amount of time a person is exposed to excessive fluoride during the critical window of development, as well as hereditary factors, affect the severity of dental fluorosis, which is dose-dependent [37]. It is thought that too much plasma fluoride prevents amelogenins from being removed during enamel maturation, which results in hypo-mineralized enamel [38]. From birth until age eight, there is a key window for dental fluorosis to develop as a result of high fluoride ingestion [39]. Therefore, dental fluorosis cannot be caused by high fluoride consumption outside of amelogenesis. Water fluoride levels above 1.5 ppm are linked to the clearly noticeable enamel alterations that are a hallmark of dental fluorosis [40].

On the other hand, fluorosed teeth have a well-mineralized outer surface. Conversely, the subsurface layer has porosities and is hypo-mineralized. Depending on its severity, fluorosis might lead to aesthetic issues in clinical settings [41]. Fluoride has an effect on ameloblasts when teeth form. Mild to moderate fluorosis is characterized by bilateral, thin, horizontal white to brown striations and stained areas. The enamel may seem pitted or discolored in extreme circumstances [42]. When they are young, patients with these types of discolorations and stains frequently visit dental offices in search of aesthetic procedures. Significant cosmetic issues in young patients may result from changes in the anterior teeth's color, shape, and structure. Combining bleaching methods with micro-abrasion may enhance the appearance of patients with fluorosis. In other words, during amelogenesis, a strictly controlled process with several stages where hydroxyapatite crystals are formed, ameloblasts are in charge of enamel creation [43]. It is unclear what the exact pathophysiology of dental fluorosis is [44].

Porous hypo-mineralized enamel is the outcome of amelogenesis exposure to elevated plasma fluoride levels [40]. In extreme circumstances, the porosity may reach the dentino-enamel interface. The stage of amelogenesis most susceptible to persistently high plasma fluoride levels is the early maturation phase [43]. Clinically, dental fluorosis can range in severity from pitted enamel that turns dark yellow-brown to nearly invisible surface-level enamel alterations that include tiny white opaque specks that the patient may not even be aware of. The majority of individuals will have aesthetic issues that draw attention to their tooth dis-colouration [45].

A yellow-brown staining of the teeth, occasionally dentine hypersensitivity, and structurally damaged enamel that becomes hypoplastic are further issues that may worry those with severe dental fluorosis [45]. The distribution of dental fluorosis is symmetrical, and the degree of damage to individual teeth within the dentition can differ [46]. Cellular proliferation and differentiation via successive epithelial-mesenchymal interactions, secretion of tissue-specific matrix proteins, transport of ions such as calcium and fluoride, and precipitation and alignment of enamel crystals via numerous interactions between organic and inorganic molecules are all components of the intricate process of enamel formation (Figure 1). These processes take place in a fluid milieu that is isolated from the bloodstream over extended periods [47].

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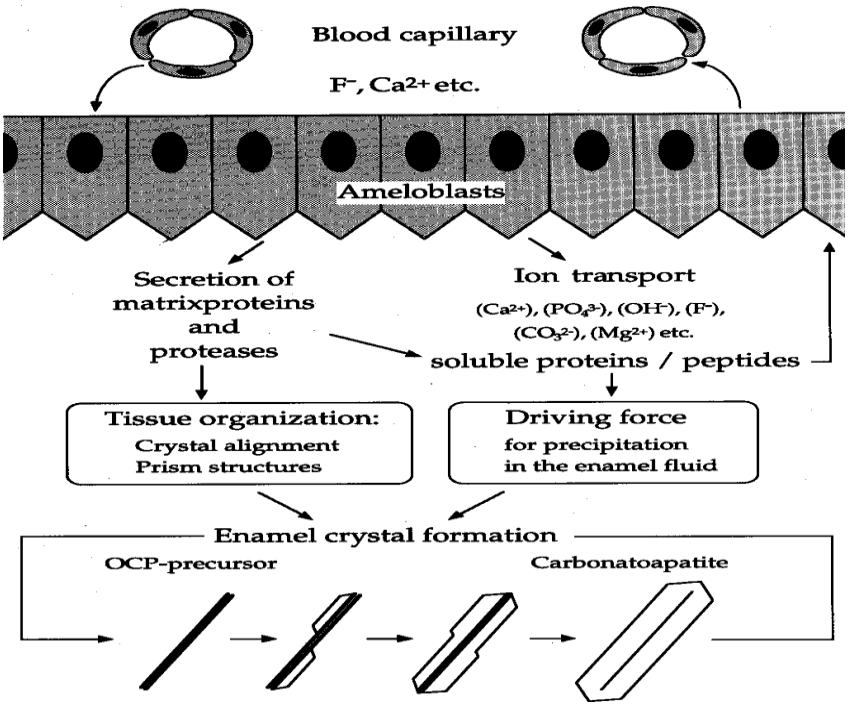

Figure 1. A schematic representation of the occasions that led to the early mineralization of enamel. From blood circulation to the extracellular space and vice versa, the ameloblasts control mass transport (such as ions and organic matter). The secreted matrix proteins and proteases, as well as different types of ions and soluble moieties, make up the mineralizing environment. Before being extracted from the developing enamel, soluble moieties are produced by post-secretory processing of the matrix proteins. The molecular makeup of the matrix proteins directs tissue organization, whereas the common ion activities in the enamel fluid act as the precipitation's driving force. Thin ribbons in shape, the initial precipitation of acidic precursors, and the subsequent epitaxial overgrowth of carbonato-apatite are characteristics of the consequent crystal formation [47].

Epidemiological status and pathogenesis of dental fluorosis

Due to several conflicting circumstances, the prevalence of dental fluorosis varies widely. From a dietary perspective, the primary cause of the high incidence of dental fluorosis is thought to be excessive fluoride in drinking water [48]. One of the main causes of the rise in dental fluorosis cases is the extensive use of foods like fluorinated beverages and fluorinated salt, which is further raising the incidence of dental fluorosis [49]. Calcium and vitamin intake may have an impact on the occurrence of dental fluorosis in children under the age of seven. A study of children with fluorosis who lived in high-fluoride locations revealed a negative correlation between the incidence and the children's dietary calcium intake. Fluorosis symptoms were successfully avoided or reduced when calcium consumption was high (>520 mg/day) [50]. According to a different study, dental fluorosis is also adversely correlated with lutein, lycopene, α-carotene, β-carotene, and carotenoids [51]; thus, consuming these nutrients may help reduce dental fluorosis symptoms.

One of the most frequent causes of enamel mottling has been identified as fluoride [52]. However, enamel mottling can also be caused by extrinsic or intrinsic causes, though they have not been found in humans. Regardless of the amount of fluoride exposure, rats with chronic acidosis and hypoxia develop enamel opacities that histologically resemble enamel fluorosis [53]. For a precise evaluation of the frequency of dental fluorosis and its epidemiology, it is therefore essential to distinguish enamel fluorosis from non-fluorotic enamel abnormalities [54,55].

However, no research has yet examined the impact of gender on the prevalence of dental fluorosis. In line with the findings of another survey of 1,044 adolescents in India [56], an epidemiological survey of 929 adolescents in Northern Colombia found that the prevalence of dental fluorosis did not significantly differ between the two genders and that it had no significant effect on the incidence [57]. Significantly, however, disparities in the prevalence may be influenced by variations in people's dietary and lifestyle choices, which can be brought about by economically undeveloped regions and the uneven status of various genders [58].

Calcium homeostasis's function in the development of dental fluorosis

According to recent research, calcium can have the following effects on ameloblast function: a) Through inositol 1,4,5-trisphosphate receptors, fluoride facilitates the release of Ca2+ from the ameloblasts' endoplasmic reticulum [59]. According to studies, in a high-fluoride environment, Ca2+ can enhance the

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inhibitory effect of fluoride on ameloblast growth, decrease apoptosis, and increase kallikrein related peptidase 4 (KLK-4) activity when compared to the control group. These effects are linked to the activation of the protein kinase R-like endoplasmic reticulum kinase–eukaryotic initiation factor 2 α-activating transcription factor 4–C/EBP homologous protein pathway (CHOP) [60].
Fluoride also has an impact on mitochondria, which are crucial calcium reserves in ameloblasts. A transmission electron microscope revealed morphological changes in the mitochondria following fluoride treatment, along with a decrease in the ameloblasts' ATP turnover rate, membrane potential, and calcium-uptake capacity. These findings suggested that fluoride impacted ameloblast homeostasis by altering mitochondrial functions [59, 61]. Additionally, the intracellular calcium signal route of ameloblasts involves the PI3K/AKT pathway. KLK-4 and amelotin levels in ameloblasts rose dramatically with a rise in calcium concentration, but PI3K, AKT, p-AKT, and FOXO3 levels sharply declined following calcium treatment [62]. However, fluoride also impacts Ca2+ transport since it lowers Ca2+ levels in fluoride-treated rats' enamel fluid, which is the space where crystals form [63]. Store-operated Ca2+ entry (SOCE), a mechanism that permits prolonged Ca2+ influx, is a crucial regulator of Ca2+ homeostasis in enamel cells [64, 65].
Therefore, it is clear that fluoride induces dental fluorosis through a variety of intricate ways. The concentration of fluoride, the length of exposure, and whether fluoride intake takes place during the formative or mineralizing stages of enamel development are factors that influence its effects [66, 67, 68, 69]. Given the varying effects of high fluoride intake on various mouse strains, it might have a hereditary component [70]. Urine is the main excretion site for fluoride, which may also have an impact on dental fluorosis models. Because rodents excrete fluoride more quickly than humans do, dental fluorosis induction in rats necessitates a larger fluoride intake [71,72].

Diagnosis, prevention, and treatment of dental fluorosis

Four sources—fluoridated drinking water, fluoride supplements, topical fluoride (particularly fluoride toothpastes), and child formula—have been found to raise the risk of dental fluorosis by studies conducted in regions with or without the addition of fluoride to drinking water. Additionally, the processed foods that some children eat can potentially significantly increase their daily fluoride intake [35]. According to a systematic review that examined 214 studies, McDonagh et al. [73] found that fluoride intake increased dental fluorosis and decreased the number of teeth with caries. Additionally, they claimed that the high incidence of dental fluorosis suggests that kids are consuming fluoride from sources other than drinking water. Dental fluorosis is frequently endemic in places where drinking water is directly drawn from deep wells, and the deeper the wells, the higher the fluoride concentration in the drinking water.
To properly diagnose fluorosis, dental surfaces must be examined in a well-lit, dry, and clean. Two-sided, diffuse (not well-defined), opaque, white striations that extend horizontally over the enamel are the hallmark of mild dental fluorosis. White patches could emerge if the opacities combine. Enamel may become pitted and/or discolored in the more severe cases. Fluorosed enamel is not stained when it first appears in the mouth; instead, stains form over time as a result of foreign ions (such as iron and copper) diffusing into the unusually porous enamel [35]. Examining the patient's medical history while taking systemic fluoride use into account can help confirm the diagnosis [74].
A useful first step in diagnosing oral epidemiology and public health issues is to distinguish between fluoride and non-fluoride disruptions of dental enamel. Descriptive indices have been proposed by a number of researchers to categorize other comparable non-fluoride enamel opacities. Nonetheless, endemic incidence, a history of consuming fluoride in drinking water at levels below optimum during tooth development, and its bilateral symmetrical pattern are thought to be crucial distinguishing characteristics for the diagnosis of dental fluorosis (Figure 2) [75].

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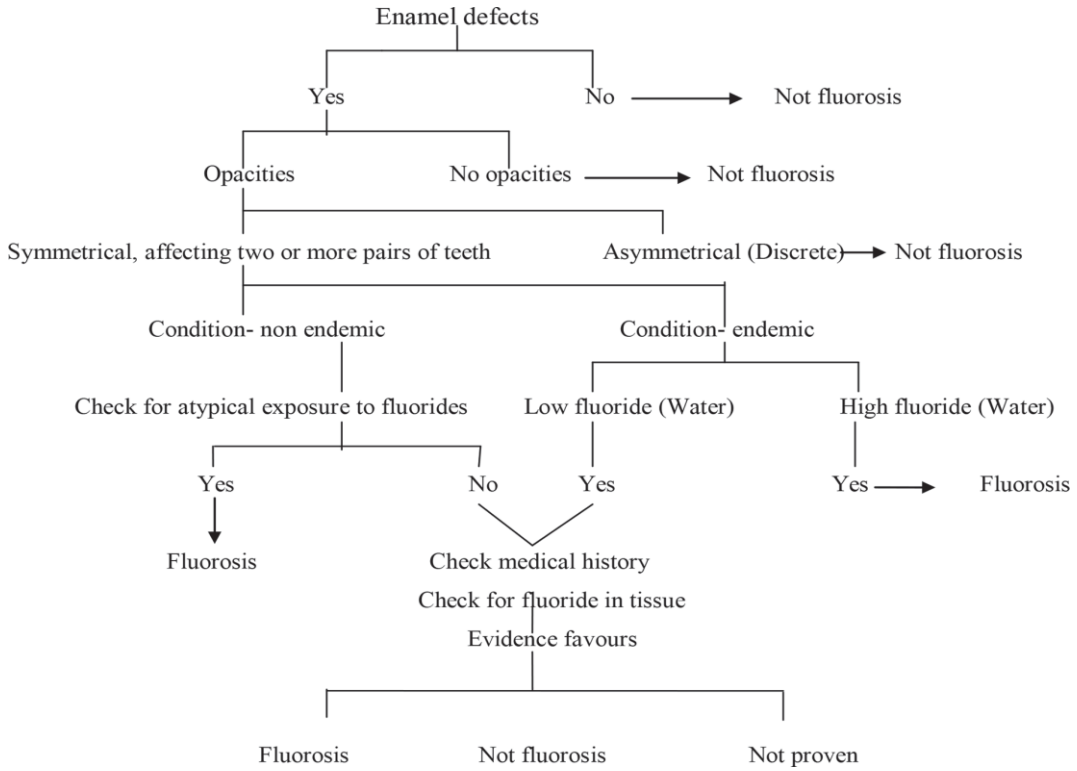

Figure 2. The recommended sequence for the differential diagnosis of dental fluorosis [75].

Basic understanding of the physiology of fluoride toxicosis, taking a pertinent history, being aware of the condition's clinical symptoms, doing a correct physical examination, and conducting pertinent investigations are all necessary for the diagnosis of different types of fluorosis. The presence of fluoride content in biological samples, such as milk, urine, blood serum, nails, teeth, hair, sweat, bones, saliva, etc., can be used to determine whether or not fluorosis is endemic or chronic fluoride intoxication in any given area. This is because these samples are excellent biomarkers of fluoride toxicity. Urine, however, is the best biomarker for evaluating fluoride toxicosis among these bio-samples since it is simple to collect noninvasively and methodically on the spot [76].

Avoiding excessive fluoride exposure during tooth development, up until the age of about eight years, can help prevent dental fluorosis. Dental fluorosis is unlikely to happen if fluoride exposure throughout pregnancy and childhood is maintained extremely low to prevent developmental neurotoxicity because the growing brain is more vulnerable to fluoride-induced toxicity than the developing teeth [77].

Furthermore, whitening, micro-abrasion, or the removal of the maturing enamel with fine polishing burs alone or in conjunction with a strong acid are the common treatments for mild dental fluorosis that is deemed undesirable. 4. Dentists typically offer more involved treatments, including as composite resins, porcelain veneers, and occasionally full coverage restorations, because in more severe situations, simple micro-abrasion may not be sufficient to remove the fluorotic enamel [78].

Therapeutically, for many years, mild-grade fluorosis has been effectively treated using McInnes solution [79]. One component, anesthetic ether, five parts hydrochloric acid (36%), and five parts hydrogen peroxide (30%) make up McInnes solution. A cotton applicator was used to apply the freshly blended solution to the tooth. Every bleaching session included applying a bleaching solution for five minutes at one-minute intervals while using a rubber dam, and then polishing the teeth with prophylactic paste [80].

For teeth with mild to moderate fluorescence and no enamel flaws, enamel micro-abrasion and vital bleaching were previously the recommended treatments [81, 82]. Traditionally, laminate veneers or crowns were used to treat teeth that had severe fluorosis or enamel abnormalities [83,84]. On the other hand, minimal intervention dentistry is the more recent approach. Even though the more conventional restorative techniques give many patients a satisfactory aesthetic appearance, minimally invasive techniques (enamel micro-abrasion and vital bleaching) may be the first choice because restorative intervention is frequently the beginning of a lengthy series of re-restorations, which typically lead to crowns and implants, regardless of how well the first restoration was prepared.

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Expectations and prognosis for tomorrow

Once developed, dental fluorosis cannot heal itself, according to the traits of enamel growth. Therefore, fluoride intake should be closely monitored throughout the crucial period of enamel formation in children under the age of seven. Fluoride consumption has the potential to cause neurotoxic and reproductive harmful consequences [85, 86] harm hard tissues, and impair the intelligence of children [87]. The pathophysiology of dental fluorosis is gradually becoming more understood as research increases. Three-dimensional cell culture technology will generate fresh concepts for subsequent investigations. However, research on the function of exosomes, circular RNAs, long non-coding RNAs, and miRNAs in dental fluorosis is lacking and needs more investigation. An essential intracellular calcium pool that contributes to intracellular calcium regulation is the mitochondria. Furthermore, a crucial area of study is the relationship between energy delivery processes and mitochondrial DNA. As more research is conducted, more strategies to prevent and cure dental fluorosis and lessen the harm it does to the general public will become available.

Conclusion

Dental fluorosis remains a significant public health concern, especially in areas with high natural fluoride levels in drinking water. The condition arises from excessive fluoride exposure during enamel development, leading to permanent aesthetic and structural changes in teeth, particularly the anterior ones. While fluoride is essential for preventing dental caries, maintaining optimal intake, especially in children under seven, is crucial to avoid fluorosis. Effective prevention relies on public education, monitoring fluoride sources, and improving nutritional status. Continued research into the molecular mechanisms and genetic factors of fluorosis will help refine both preventive and therapeutic strategies.

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Conflicts of Interest

The authors declare no conflicts of interest.

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المستخلص

تسمم الأسنان بالفلور هو اضطراب في نمو مينا الأسنان، ينتج عن الإفراط في تناول الفلورايد أثناء تكوين الأسنان، وخاصةً بين سن 20 و36 شهرًا. تظهر هذه الحالة بشكل رئيسي كتغيرات جمالية، وخاصةً في الأسنان الأمامية، تتراوح من خطوط بيضاء خفيفة إلى بقع بنية شديدة وتآكل في مينا الأسنان. الفلورايد، الموجود طبيعيًا في الماء ومصادر غذائية مختلفة، يصبح ضارًا عند تناوله بكميات زائدة، وخاصةً في المناطق ذات مستويات الفلورايد الطبيعية العالية. تعتمد شدة تسمم الأسنان بالفلورايد على عدة عوامل، بما في ذلك تركيز الفلورايد، ومدة التعرض، والحالة الغذائية، والاستعداد الوراثي. تتضمن الفيزيولوجيا المرضية اختلال وظيفة خلايا المينا وتغير إشارات الكالسيوم، مما يؤدي غالبًا إلى مينا مسامي ونقص في المعادن. على الرغم من فوائد الفلورايد الموثقة جيدًا في الوقاية من تسوس الأسنان، إلا أن الإفراط في تناوله يرتبط وبائيًا بزيادة انتشار التسمم بالفلورايد. يتضمن التشخيص الدقيق الفحص السريري ومراعاة تاريخ الفلورايد الجهازي. تشمل الاستراتيجيات الوقائية التحكم في التعرض للفلورايد في مرحلة الطفولة المبكرة، وخاصةً من خلال استهلاك مياه نظيفة والاستخدام المناسب للمنتجات المفلورة. يقتصر العلاج الحالي على الجانب التجميلي، ويتضمن إجراءات مثل التقشير الدقيق والتبييض. هناك حاجة إلى أبحاث مستقبلية لفهم الآليات الجزيئية لتسمم الأسنان بالفلورايد بشكل أعمق، واستكشاف أساليب وقائية وعلاجية جديدة.

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