Fluoride Exposure in Early Life as the Possible Root Cause of Disease In Later Life

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Fluoride, one of the most celebrated ingredients for the prevention of dental caries in the 20th century, has also been controversial for its use in dentifrices and other applications. In the current review, we have concentrated primarily on early-life exposure to fluoride and how it may affect the various organs. The most recent controversial aspects of fluoride are related to toxicity of the developing brain and how it may possibly result in the decrease of intelligence quotient (IQ), autism, and calcification of the pineal gland. In addition, it has been reported to have possible effects on bone and thyroid glands. If nutritional stress is applied during a critical period of growth and development, the organ(s) and/or body will never recover once they pass through the critical period. For example, if animals are force-fed during experiments, they will simply get fat but never reach the normal size. Although early-life fluoride exposure causing fluorosis is well reported in the literature, the dental profession considers it primarily as an esthetic rather than a serious systemic problem. In the current review, we wanted to raise the possibility of future disease as a result of early-life exposure to fluoride. It is not currently known how fluoride will become a cause of future disease. Studies of other nutritional factors have shown that the effects of early nutritional stress are a cause of disease in later life.

***Key words**: Fluoride, Growth and Development, Thyroid Gland, Mental Retardation, Caries, Autistic Disorder.*

INTRODUCTION

The mouth is the gateway for the intake of all foods and drinks into the body. When the general consumer realized that the various foods and drinks ingested in daily life may have important implications for health, they began to pay more attention to each nutritional ingredient. "Natural" has become the influential word in the consumer's decision as to whether to buy a particular food or not.

If one does not maintain healthy teeth due to dental caries and/or due to periodontal diseases, foods can't be masticated well, which may result in an excess burden to the other organs in order to digest. The decreased oral function may result in reduced intake of various nutrients such as vitamins, minerals, and protein, and, more importantly, may cause a tendency to avoid fiber-containing foods, which are critical for maintaining healthy dietary habits. These nutritional factors could affect the functional roles of the mouth, leading to an increased vulnerability to many chronic diseases and eventually influence the health status of certain organs as well as the body in general.

When fluoride was discovered to prevent dental caries [1], it was hailed as one of the greatest discoveries of the 20th century. Since then, there have been numerous reports that fluoride may possibly be associated with health-related problems. In this review, we would particularly like to consider how exposure to fluoride during the early growing period could possibly influence the physiological status of human organs.

Mechanism of fluoride action in dental caries [2]

Dental caries is due to carbohydrate metabolism in an oral biofilm by plaque bacteria to produce lactic acid. As the pH falls to about 5, calcium phosphates begin to dissolve from the enamel apatite mineral and produce porosity. This is the earliest stage of carious lesion formation, known as white-spot lesions. Remineralization occurs as the overlying plaque pH returns to neutrality. The released PO_4^{3-}, OH^- and CO_3^{2-} anions buffer and eventually halt mineral loss. Together with salivary buffering, this causes the pH to rise and reverse the porosity, as mineral is re-deposited in the partially demineralized tissue. However, buffering can be overwhelmed if the pH drops to or below 5.

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Thus, dental enamel demineralizes by the net movement of ions out of a mineral phase and into solution. Dental enamel remineralizes by the net movement of ions out of solution and into a mineral phase. Such cycles of de- and remineralization occur several times a day. Whether or not this leads to the development of frank caries and cavity formation depends on the dominant process [3].

Genetic, congenital, and developmental processes, along with environmental factors all affect mineral chemistry by altering the solubility of the apatite crystallites, as well as by affecting the thickness and smoothness of the enamel layer. Enamel structure, diet, state of health and oral habits are additional variables that determine the chemical environment surrounding enamel crystals, and determine the balance between dissolution and remineralization. Degree of crystallinity and crystallite size are major contributors to enamel solubility. Amorphous (0% crystallinity) phases dissolve more rapidly than those with a high degree of crystallinity, and more rapidly the smaller the crystallite size.

Fluoride ion is highly electronegative and strongly affects these factors by binding and removing acid H^+-ions from the demineralized hard tissue, catalyzing mineral re-deposition, and formation of the more acid-resistant, fluoridated form of apatite. A dose-response relationship between the concentration of fluoride and the cariogenic loss of enamel has been reported many times, perhaps most recently by Creeth *et al* [4]. One of the interesting features of remineralization is that enamel that has been demineralized and then remineralized, is more resistant to subsequent acid attack than it was initially [5].

The opportunity of the fluoride exposures in early life

Fluoride is contained in natural foods such as brewed black tea, raisins, and white wine[1]; decaffeinated tea contains more fluoride than that of caffeinated tea [6]. Some communities in the United States not only add fluoride to the drinking water, but supplemental tablets of fluoride are still available to general consumers.

The prevalence of dental fluorosis has increased in the U.S., Canada, and other nations due to the widespread ingestion of fluoride during the first three years of life [7]. In the first few months of life, daily fluoride intake of infants may be significantly higher than the optimum [8].

More than 90% of the toothpastes in the U.S. contain fluoride and many children are exposed to fluoride through incidental ingestion of toothpaste [9]. For children 1–3 years, 30–75% of the dentifrice is ingested, and for children 4–7 years, 14–48% is ingested [10].

Each tube of toothpaste displays the warning "Keep out of reach of children under 6 yrs. of age. If more than used for brushing is accidentally swallowed, get medical help or contact a Poison Control Center right away." Many children accidently swallow toothpaste [9], fluoride gels for topical applications, and mouthwashes [6,11]. Between 1994 and 2011, calls to Poison Control Centers due to toothpaste ingestion increased approximately seven times [12,13].

For 2013-2014, as part of ongoing National Health and Nutrition Examination Survey, the data were released in the public (14). According to this survey, about 30% of the children were at the risk of dental fluorosis. Younger children generally ingest a higher proportion of toothpaste than older children, ingesting over half of the toothpaste per brushing [7,15]. Some children ingest more than 1 gram of dentifrice per brushing (1 mg of fluoride) [16] Toothpastes specifically flavored for children have been linked to the use of larger quantities of toothpaste than suggested, increasing the importance of the pathway of excessive fluoride intake [17]. Additive effects by ingesting toothpastes results in 5.56 times likely to develop fluorosis [18], and timing and fluorosis are closely associated [19].

Among children aged 12 and 24 months, the amount of fluoride ingested from toothpastes could constitute a substantial proportion of the total daily intake of fluoride [20] and again among young children from 2 to 7 years of age [11]. Thus, if one starts brushing teeth from a young age, it is likely that one will develop fluorosis [21].

Boiling water doubles fluoride concentrations found in non-boiled water [22], suggesting that foods or infant formula prepared with boiled water may result in increased fluoride intake through diet [9].

Children growing up in ethnic communities with frequent tea consumption may have increased high intake of fluoride [9]. Certain areas of the U.S. have shown the incidence of fluorosis in the range of about 70% [23] to 80% [24] in children. This simply indicates a very high incidence of fluoride's adverse effects on growing children.

Prenatal fluoride supplementation (100 PPM) in drinking water in an animal study has shown to increase fluoride concentrations in plasma, mandibular incisors, and femoral epiphyses of rat pups by 25, 36, and 38% respectively, when given during pregnancy [25]. This study clearly indicates that both bones and teeth of fetuses take up fluoride during growth and development in pregnancy.

Based upon the animal study [26] and human [27], Chan *et al* [26-28] have found that plasma levels of fluoride in the presence of caffeine was significantly higher than that of fluoride alone, suggesting that the presence of fluoride would remain longer due to the ingestion of caffeine-containing beverages. They hypothesized [28] that the increase of the fluorosis may partly explain the presence or intake of caffeine and fluoride concomitantly. Therefore, according to their hypothesis, theoretically, babies born to pregnant mothers who are heavy coffee drinkers (coffee contains caffeine on the average of approximately 100 mg/ cup of coffee and soft drinks contain caffeine approximately a little less than half of the cup of coffee) and/or habitual drinkers of caffeinated beverages must have a much greater chance of fluorosis in the future than babies of mothers who do not drink caffeinated drinks during pregnancy. According to the recent findings that higher fluorosis severity was associated with soft drink consumption as most soft drinks contain caffeine [29].

Incidences which we cited clearly suggest that there are numerous opportunities for fluoride exposures in fetuses, newborns and/or children in early life. Much of the literature is primarily concerned with the adverse effects of fluoride ingestion resulting in fluorosis. However, in the U.S., fluorosis has been considered primarily as an esthetic problem [9].

It is unfortunate that we are not more concerned with the consequences of fluoride exposures to the general health of children. This may possibly include other organs such as brain, bone, and thyroid gland development affected by the ingestion of fluoride in early age.

Critical period of growth in development

Enesco and Leblond [30] defined the three stages of growth. First, growth of organs is due to rapid cell proliferation in cell number as a period of hyperplasia [31]. This period of rapid cell division is called the critical period of growth [32] Second, cell proliferation continues at a slower rate and cell size increases. Third, cell proliferation stops while cell enlargement (in cell size) proceeds as a period of hypertrophy [31].

The patterns of the increased number of cells in the early growth period are different among the organs [33]. For example, the increased cell number will cease much earlier in the brain than that of the salivary glands as is shown [33]. This indicates that the critical growth period is different from organ to organ. This is why when early nutritional stress is applied during a certain time of the growth period, some organs would be affected more than others. Importantly, once a certain nutritional stress, such as undernutrition, is applied during the critical period of growth when cell number is primarily increasing, animal studies show that it is difficult to recover the full extent of normal size even if full nutrition is applied in later life [34]. It was also shown in humans that children who had been undernourished from infancy were still behind in mental development in later life [35].

Excessive intake by the young of an ingredient such as fluoride, which is found in most toothpastes and also in other substances, could result in one of the nutritional stresses during the critical growth period. Some of the body's "memories" of early fluoride exposure may become translated into pathology and thereby determine disease in later life [36].

Fluoride and Intelligence quotient (IQ)

Prenatal exposure to various substances that might not be toxic to adults, but could cause neurobehavioral deficit in children [37]. Therefore, the developing brain tends to be much more susceptible to nutritional stress than the adult brain. Some neurodevelopmental disorders are reported to be learning disabilities, sensory deficits, and developmental delays [38]. Subclinical stages of these disorders might also be common [37]. If the developmental process is inhibited, the consequences could be permanent [39]. In a 2006 study, fluoride is mentioned as a possible factor which might affect brain development, and further in-depth studies were suggested [37]. Since then, fluoride has been identified as a developmental neurotoxicant [40].

Children who consumed water with higher levels of fluoride (water fluoride: 2.47±0.79 mg/L; range: 0.57–4.50 mg/L) reported significantly decreased IQ compared to that of children who consumed water with lower levels of fluoride (water fluoride: 0.36±0.15 mg/L; range: 0.18–0.76 mg/L) in China [41]. As the fluoride level in drinking water increased, the IQ fell and the rates of mental retardation and borderline intelligence increased. Furthermore, the children's IQ and their parents' education level and family income do not show any association [41].

These decreases of IQ from the higher contents of fluoride in the drinking water consumed during the growing period have also been reported in India [42,43], Iran [44] and among the frequent tea-consuming children in Taiwan [45]. Systematic reviews and meta-analyses have suggested the possibility of an adverse effect of high fluoride exposure on children's neurodevelopment [46].

The blood-brain barrier that protects the adult brain is not completely formed until about 6 months after birth [37] Fluoride is reported to cross the blood-brain barrier [47,48]. It is conceivable that this results in the impairment of the developmental process of the nervous system of the fetal and early postnatal infant. This is a critical period of growth when cells are primarily proliferating. The human brain also develops postnatally, extending over many months, through infancy and into early childhood [37]. In endemic fluorosis areas, drinking water fluoride levels greater than 1.0 mg/L may therefore adversely affect the development of children's intelligence [41]. However, one study [49] disputes the findings of fluoride intake and IQ.

Fluoride and autism

Autism, which is one of the neurodevelopmental disabilities [40], affects many children and seems to be increasing in incidence. Since 2006, Grandjean and Landrigan [40] have identified fluoride as one of the developmental neurotoxicants. Fluoride produces neuronal destruction and synaptic injury which involves free radical and lipid peroxidation [50,51] and the inhibition of critical antioxidant enzymes [52].

The greatest fluoride accumulation occurs in the hippocampus, which is time- and dose-dependent [52]. For children and young adults, early-life exposure to fluoride could become the root of the development of neurodegenerative disease in later life [40].

Fluoride and pineal gland

Tapp and Huxley [53] examined calcium contents of various age group from pineal gland. They have found that significant amounts of calcium are present in the pineal glands of children. Further, the higher weights of female glands could be accounted for in part by their higher calcium content.

The pineal gland is a mineralizing tissue and the calcified concretions are composed of hydroxylapatite (HA) [54]. It is likely that extremely high level of substitution in the crystal structure of pineal HA by fluoride. The Aged human pineal gland was found the positive correlation between fluoride content and calcium of the pineal gland [54]. Apparently fluoride accumulates freely in the pineal gland, although the amount of fluoride present differs from one sample to others. Therefore, it is likely the age independence of pineal calcification.

The pineal gland produces melatonin, a hormone related to setting the rhythms and duration of sleep. The degree of calcification has been associated with a decreased secretion of melatonin [55]. Thus, this could result in the disturbance of circadian rhythms and sleep patterns [56].

Fluoride exposures in childhood and bone diseases

Chen *et al* [57] reported that by supplying low fluoride drinking water in southern China, various bone metabolism indicators such as calcitonin and serum osteocalcin levels, returned to normal levels among the 6-12 age group of children. Osteosarcoma, a rare malignant bone tumor most commonly occurring in children and young adults, is reported to be associated with higher serum fluoride levels [58] and high fluoride bone content [59] This may suggest the role of fluoride in osteosarcoma.

An association between fluoride exposure in drinking water during childhood and the incidence of this disease among males has also been reported [60]. On the other hand, a case-report study concluded that there is no increased risk for osteosarcoma from exposure to fluoride [61]. By reviewing bone tumors in children and young adults [62], certain associations between high fluoride and osteosarcoma have been described in epidemiological studies. However, the authors emphasized that further research is needed to confirm or refute these putative risk factors.

Fluoride and thyroid gland

A clear relationship between fluorosis and iodine deficiency disorders was recently shown for the first time [63]. Because fluorosis is also prevalent in our society [23,24], these children have shown dental fluorosis symptoms that may need to be investigated in relation to

thyroid stimulating hormone (TSH) and thyroid hormones, freeT4 and freeT3.

It should also be noted that even in some of the children in the control group who consumed "safe" water (<1.0 ppm F–), fluoride levels in blood and urine were above current upper limits. This indicates fluoride ingestion, from foods and beverages and dental products such as toothpaste. In those children, disturbances in thyroid hormone ratios have been observed [63].

Hypothyroidism in the mother resulted in lowered IQ in the offspring (64). Hearing impairment in children ingesting high fluoride and living in endemic areas of iodine deficiency is reported [63]. It has recently been reported that the serum fluoride concentration had a significant relationship with thyroid hormone (FT3/FT4) and TSH concentration among 8-to-15-year-old children [65].

Fluoride and possible fetal origins of adult diseases

Disease may originate in utero. Fetal nutrition plays an important role for newborns and affects health during child- and adulthood [36,66]. It is well reported in epidemiological studies that undernourished babies will more likely develop various disease in later life. For example, low rates of growth before birth are linked to the development of coronary heart disease, stroke, diabetes, and hypertension in later life [36,67]. These associations are explained by a phenomenon known as programming. "Programming" occurs when an early stimulus or insult, operating at a critical or sensitive period, results in permanent or long-term changes in the structure or function of the organism (68). The lasting changes in structure and function are often caused by one of the nutritional stresses acting at critical periods of growth during the early developmental period (36).

It has been reported that early overfeeding may lead to programming later obesity, and that breast-fed and bottle-fed baboons have long-term differences in their lipid metabolism and in the degree of atherosclerosis [68].

The past literature, as we pointed out, suggests that there are many possibilities where fetuses, newborns, and/or children may be exposed to fluoride in early life during the critical period of growth. Nevertheless, it is unfortunate that many emphases placed on the resulting fluorosis of developing teeth were mainly concerned simply as an esthetic problem. It is probable that early dietary status may become the root of the development of possible disease states in general.

Fluorosis was considered as a result of fluoride effects on amelobasts cells where tooth enamel is deposited. If then, it is quite natural to raise the question as to whether or not different cells from other organs in the body could be affected by fluoride exposures. Furthermore, it might be worthwhile to speculate that symptoms might not appear right away at the time of exposure, or were programmed [68] due to fluoride, and underlining effects could eventually appear in later life.

Then it would not be a surprise that the sources of adult diseases may originate from this critical time by fluoride exposures already in utero as one of the cause effect. If the root of adult disease is already seeded by the exposures of fluoride during this period, one can even argue that fetal, newborn and childhood nutritional environment is as important as adult dietary habit and lifestyle. Therefore, a woman who is planning to have babies may require careful nutritional guidance as one of the most important pieces of advice from nutritionists and/or dietitians.

We do not know the mechanism of how fluoride leaves lasting imprints on the body and how it gives rise to possible diseases in later life. From the prenatal study with animals [25], it is apparent that fluoride will pass through utero-placental blood flow and has accumulated in the mandibular incisor and epiphysis during pregnancy.

Genetic influences on adult bone size and mineral density may be modified by undernutrition in utero. Intrauterine programming could contribute to the risk of osteoporotic fractures in later life [69].

In an earlier animal study, relatively small amounts of caffeine were fed during pregnancy, and during the growing period until adulthood. Then the caffeine diet was replaced with a non-caffeine diet. Some animals showed permanent altered hyperactive behavior as the animals aged [70].

When exposed to caffeine only during the gestation and lactation periods, reduced locomotive activity was recorded in the later ages of animals exposed to caffeine [71]. These examples also suggest that certain nutritional factors in the early growth period might exert critical influence on behavior in later life. Therefore, as we speculate, it is not surprising that fluoride exposures in early life could influence or originate the root-cause of certain diseases in later life.

Although it is well established that a dentifrice containing fluoride is one of the means of incidental intake among the young, recent introduction of a theobromine-based dentifrice [72] may provide caries protection while minimizing the risk factor of children exposed to fluoride during this period.

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