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Chronic Fluorosis: A Disease of Concern

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ABSTRACT

Introduction: Chronic fluorosis is a widespread disease caused by ingestion of high levels of fluoride through drinking water and food. Fluoride content in food depends on its concentration in water, soil and air.

Aim: This review article is aimed at providing information about fluorosis and its ill effects.

Objective: The objective is to address the adverse effect of fluoride on several organ systems besides the more commonly known skeletal and dental manifestations.

Methodology: A detailed search of related literature has been carried out with the help of search engines. Pub Med and Research gate have been used for obtaining authentic information.

Discussion and Conclusion: This review article summarizes the major deleterious health problems caused by fluoride and emphasizes that fluoride mitigation needs to be practised widely since fluorosis is a preventable disorder.

Key Words: Fluoride, Fluorosis, Toxic effects, Diabetes, Thyroid abnormalities, Cardiovascular system

INTRODUCTION

The 13th most abundant element in the earth's crust is Fluorine.¹ It is only a microelement for human health but is one of the most significant endotoxins which appear in the environment.² Fluoride is one of the few elements that have been shown to cause significant effects by various means such as through drinking water, air, dental products, food and beverages. Excessive fluoride in water and soil is mostly of geological origin which can be further compounded by over-exploitation of groundwater resources and Industrial pollutants.

After absorption from the gastrointestinal tract (GIT), the ability of fluoride ions to easily penetrate the cells through the membrane results in affecting various functions by altering the activity of enzymes and hormones.^{3,4} Fluoride not only accumulates in the bones and teeth but also gets deposited in the soft tissues.⁵ The level of fluoride, considered safe for humans is 1-1.5 mg/L while, prolonged ingestion is associated with dental fluorosis, skeletal fluorosis and several other disorders due to its ability to inhibit the proliferation

of cells. It should be noted, however, that while Micromolar Fluoride ion concentrations promote the growth and proliferation of cells, millimolar concentrations suppress cell proliferation and induce apoptosis in the hard tissues.⁶⁻⁹ Many metals such as lead, copper and manganese can interact with Fluoride ion and contribute to increased accumulation of toxic elements and micronutrient deficiency in mammals.^{10,11}

Effect on bones and teeth

Fluoride has proved to be highly effective in the prevention of dental caries. It gives long-lasting protection against dental decay. Regular fluoride exposure at the time of teeth development contributes to protection against dental decay. Plaque bacteria form organic acids, which dissociate releasing H⁺ ions and lower the pH in areas surrounding the tooth and finally leads to the release of calcium from the tooth.¹² Fluoride inhibits this demineralization and thus has a dental caries protection potential. Fluoride also has an antimicrobial effect as it inhibits carbohydrate metabolism in *oral streptococci* and *lactobacilli* as it inhibits the enzymes enolase and adenosine triphosphatase.^{13,14} Though, it has

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beneficial effects on teeth and bones when present in low concentrations, excessive intake gives rise to adverse effects from dental fluorosis to the crippling skeletal fluorosis depending on the level of fluoride and the period of exposure. As the fluoride ion is strongly electronegative, it is attracted to the positively charged Ca ions in the teeth and bones.¹⁵ Fluoride alters the resorption of bone tissue and affects the homeostasis of bone mineral metabolism. Fluoride ion reacts with crystals of hydroxyapatite and forms a scaffold for the bones. A combination of osteosclerosis, osteomalacia and osteoporosis in varying degrees characterizes the bone lesions.¹⁶

The high affinity of Fluoride ion to mineralized tissues results in the high Fluoride ion concentrations in bones and teeth and so these materials are used as a bioindication of long term exposure to Fluoride.^{17,18} the earliest sign of chronic fluoride exposure is the characteristic mottling of dental enamel.

Effect on Thyroid Function

Excessive amounts of Fluoride interfere with the functioning of the thyroid gland. The thyroid gland is the most sensitive organ to the effect of fluoride.¹⁹

Since fluoride is more electronegative than iodine, it easily displaces iodine and thus affects the functioning of the thyroid gland. It is regulated by a negative feedback mechanism i.e. when the pituitary gland senses a drop in $F T_3$ levels in circulations; it releases more TSH which stimulates the thyroid gland to accelerate the production of T_4 . The Source of T_3 is from peripheral deiodination of T_4 . The enzymes which bring about deiodination are known asiodothyronine deiodinases and fluoride interfere with the activity of the deiodinases.^{20,21} Thus, Fluoride increases the concentration of TSH and decreases the concentration of T_3 and T_4 hormones.

Effect on thyroid function was associated with a fluoride exposure level of 0.05 – 0.13 mg/kg/day when iodine intake was adequate and 0.01 – 0.03 mg/kg/day when iodine intake was inadequate.²²

Effect on melatonin production

Animal studies on the effect of fluoride exposure to pineal glands show that it results in altered melatonin production and acceleration of sexual maturity. The reduced Melatonin production can impair the sleep-wake cycle. However, no studies on humans have been demonstrated.^{23, 24}

Effects on Insulin secretion and Diabetes

Various studies have shown that insulin resistance in humans develops due to chronic fluoride exposure.^{23,24} Impaired glucose metabolism is associated with a serum fluoride concentration of 0.1 ppm or greater.^{25,26} Hyperglycemia induced by fluoride is mainly due to an increase in hepatic glycogenoly-

sis.²⁷ Fluoride inhibits the glycolytic pathway by inhibiting enolase resulting in increased accumulation of two phosphoglycerates which is equilibrated by three phosphoglycerate enzymes being phosphoglucomutase. As a result, blood glucose levels increase.²⁸ Moreover, diabetic patients tend to consume larger quantities of water and this further leads to fluoride accumulation.²⁹ This in turn leads to impaired renal function, increased capillary permeability and microcirculatory defects.^{30,31} Invitro experiments on isolated Islets of Langerhans cells showed that the basal, as well as glucose-stimulated insulin, was found to be repressed as the fluoride concentration was increased.³¹

Fetal defects

Fluoride can cross the placental barrier into fetal tissue. It can affect the fetal brain tissue and this can cause neurological damage, neuronal degeneration and reduced secretion of norepinephrine. Fluoride also disrupts nerve cell receptors which can result in neural dysplasia.³² Fluoride has been found in the amniotic fluid in pregnant women living in areas of high fluoride concentrations and this result in fetuses being exposed to elevated fluoride levels.³³

In mammalian cells, fluoride causes genetic damage through chromosomal aberrations at cytotoxic concentrations (≥ 10 mg/L) which may be due to the interaction of enzymes responsible for DNA synthesis or repair.³⁴

Effect on brain

A few epidemiological studies have shown lowered IQ levels in children exposed to 2.5 to 4 mg/L of fluoride in drinking water.³⁵ Fluoride also tends to increase free radical production in the brain which may have a bearing in increasing the risk of developing Alzheimer's disease and dementia.^{22,36} Experiments on mice have shown that chronic exposure to Fluoride brings about changes in learning, memory as well as neuropathological injury. It also raised the number of senile plaque, decreased levels of synaptic proteins and caused inflammation in the brain. This in turn could lead to an increased risk.³⁷

Effect on Reproductive health

Lowered fertility rates have been implicated with increased fluoride levels as prolonged fluoride exposure is associated with increased levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and brings about decreased estrogen levels.³⁸⁻⁴⁰

Prolonged exposure to fluoride also leads to decreased testosterone levels and delay in its conversion to potent metabolites, disturbed androgen to estrogen ratios as well as estrogen receptor to androgen receptor ratios.⁴⁰ This effect on reproductive health is further compounded due to reduced thyroid hormones.^{41,42}

Haematological effects

Chronic fluoride exposure brings about haematological effects such as anaemia, eosinophilia and dysplastic changes on granulocytes in the bone marrow.⁴³ Fluoride is also known to destroy probiotics in the gut, resulting in decreased production of Vitamin B12 which is required for Hemoglobin synthesis.⁴⁴

Effect on Renal system

The kidney has a major role to play in the excretion of fluoride and the kidney tubules are also damaged due to uptake of fluoride.⁴⁵ Prolonged exposure to high levels of fluoride increases the probability of developing renal diseases due to the structural and functional changes in the kidney such as swelling, degeneration of tubular epithelium, fibrosis and tubular necrosis. This in turn leads to increased serum creatinine and urea nitrogen.⁴⁶

Effects on Gastrointestinal tract (GIT)

High concentrations of fluoride react with hydrochloric acid in the stomach to form hydrogen fluoride. The excessive formation of hydrofluoric acid results in irritation of the gastric mucosa.⁴⁷ As, Fluoride also stimulates secretion of gastric acid this, will diminish the blood supply in the stomach lining, resulting in death of epithelial cells in the GIT. Though, this observation has not been well documented in humans, adverse GIT symptoms are seen in areas of endemic fluorosis especially when the quality of nutrition is poor.⁴⁸

Central Nervous System

Fluoride can cross the blood-brain barrier before birth and is believed to affect mental development. This can result in learning disorders and decreased intelligence in children. Reports of decreased levels of neurotransmitters have been seen in fluoride endemic areas.⁴⁹

Fluoride brings about degenerative changes in the neural tissue which can lead to decreased memory and learning ability.⁴⁶ The effect may be further compounded by deficiency of some elements such as iodine or the presence of other neurotoxic compounds as pollutants.⁴⁹

Effect on Immunity

Chronic fluoride exposure affects cell-mediated and humoral immunity as it destroys white blood cell energy reservoirs thus affecting phagocytosis and inhibition of antibody formation.⁴⁶

Effect on Reproductive system

The effect of fluoride on the reproduction system has not been investigated in detail though fluoride was indicted for decreased birth rates.⁵⁰ In one study, an interesting observation was that organic farmers who avoided pesticides

were found to have double the average sperm density when compared to other farmers who used pesticides treated with fluoride.⁵¹ High Fluoride levels are also known to be associated with reduced Testosterone levels.⁵²

Effect on Cardiovascular system

Chronic fluoride exposure promotes inflammatory mechanisms. This in turn can lead to atherosclerosis and myocardial cell damage as oxidative stress, along with inflammation are important mechanisms involved in ischemic stroke. Fluoride also interferes with numerous enzymes resulting in elevating the risk factors for cardiovascular diseases besides, causing degeneration of the heart muscle.⁵³⁻⁵⁵ ECG of patients with dental fluorosis showed that a significant percentage of them had abnormal heart rhythms.^{56,57}

Anaesthetic concerns in chronic fluorosis

In patients with fluorosis, there may be difficulty in intubation during anaesthesia due to the rigid cervical spine which is compounded with the limitation of movements of the intervertebral joints.^{58,59} There is also a greater degree of risk for postoperative respiratory complications due to restricted chest movement.⁵⁸⁻⁶⁰

CONCLUSION

Though fluorosis is a preventable disorder, it is unfortunately linked to several abnormalities which require attention. The various linked disorders of fluorosis need to be addressed. Combating fluorosis can be achieved by bringing about awareness, motivating and disseminating knowledge to the public on the avoidance of fluoride contaminated drinking water, arrangements of alternate sources of water, provision of fluoride-free drinking water, improving nutritional status and health education. Though some progress has been made, there is still a lot left to do. This review article is an attempt to disseminate information among medical practitioners and public health specialists.

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Conflict of interest

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