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Fluaoride and Its Health Impacts-A Critical Review

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Abstract: *Fluorine is a biologically important trace element .In its ionic form fluoride, it is beneficial because the role it plays in bone and teeth mineralization. However this beneficial effect is felt when the fluoride concentration is low. At higher concentration the adverse effects of fluoride far out way its beneficial effects. Millions of people all over the world presently suffer from a debilitating bone disease called skeletal fluorosis and also from dental fluorosis. Apart from dental and skeletal fluorosis fluoride also affects many vital organs of the body. Scientists and Doctors across the world have worked extensively on the health impacts of fluoride on humans and animals and found that fluoride has tremendous impact on the living system.In this review the authors have made a holistic approach to highlight the impact of fluorosis on the entire body rather than confining the same to only bone and teeth.*

Key words: *Fluorosis, Fluoroapatite,Biomineralisation,Calcification, Osteosclerosis.*

I. Introduction

Fluorine, a trace element in biological system, is considered essential for animals and humans as it is involved in structural use, especially in the biomineralisation of bone and the enamel of teeth. The ionic radii of hydroxyl ion (r =133 pm) and fluoride ion(r =129 pm) being comparable, replacement of hydroxyl (OH^-) group in hydroxyapatite [$Ca_5(PO_4)_3(OH)$] by fluoride ion(F^-) forms fluoroapatite, a compound which strengthens the teeth against attack by organic acids produced by the fermentation of organic substances in the mouth. Thus it prevents the incidence of dental caries .The actual role of fluoride in preventing the incidence of dental carries is much more complex. It is suggested that it may inhibit the bacterial enzymes to reduce the production of organic acid through fermentation. It has been noted that fluoride concentration below 0.5 ppm reduces dental carries among the children. The presence of fluoride in drinking water is also found to curtail the incidence of osteoporosis, a disease among the aged people, which causes a reduction in the density of bones. It is believed that formation of fluoroapatite makes the bone more resistant to decay. [1]

In fact the beneficial role of fluoride is felt at low concentration, but at higher concentration of fluoride i.e. above 1.5 ppm it adversely affects the living system. Adequate levels of fluoride for different age groups are given in the table below [2].

Table: 1(Adequate levels of fluoride for different age Groups)

Sl no	Age Group	Duration of Intake	Amount of intake in mg /day
1	Infant	0 - 6 months	0.01 mg/day
2		7 - 12 months	0.5 mg/day
3	Children	1 - 3 years	0.7 mg/day
4		4 - 8 years	1 mg/day
5	Boys/girls	9 - 13 years	2 mg/day
6		14 - 18 years	3 mg/day
7	Males	19 and above	4 mg/day

Excess fluoride may lead to an increased demineralization leading to the precipitation of Calcium phosphate and Calcium fluoride and it interferes with calcium metabolism. Thus excess fluoride intake can initiate an erratic Calcium metabolism which results in deformed bones and mottling of teeth. Prolong ingestion of fluoride into the body system above the recommended level leads to a dreaded, crippling disease called Fluorosis which include dental and skeletal fluorosis apart from thyroid problems, growth retardation, kidney damage, heart attacks etc.

In fluorosis, due to the substitution of active OH- group by F- some enzymes like enolose, pyrophosphatase become inactive. Fluoride concentration greater than 3ppm in drinking water may cause dental fluorosis (indicated by weakening of tooth enamel, development of brown or yellow patches on the teeth). Intake of fluoride above 20ppm may lead to severe toxicity like osteosclerosis(in which 50% of the OH- group in [$Ca_5(PO_4)_3$ (OH)] is replaced by F- in bones). It leads to skeletal fluorosis and hypercalcification. Consequently the bones of limbs joints, pelvis, and spine are severely damaged. In fluorosis even the ligaments of spine and collagen of bones are calcified and the patients are crippled due to stiff joints [1].

II. Fluoride Cycle And Living System

Fluoride is drawn from soil, water and nutrients by plants. Both human beings and animals are subjected to fluoride intoxication since they take fluoride contaminated water and food at different levels. Fluoride enters the human body mainly through respiration and ingestion. Approximately three fourth of the daily intake of fluoride by humans and animals returns to the atmosphere through excretion in the form of urine and dung while the rest is accumulated in the bones of the body system.The rest of the fluoride, which could not be excreted, remains even after the death and decay of animals and plants and is released into atmosphere through decomposition by micro organisms. The regenerated fluoride then passes into the consumers directly or indirectly through the food chain and ultimately fluoride finds its way into the body system repeatedly as an abiotic component even after death and decay. Approximately 75–90 per cent of ingested fluoride is absorbed in the blood out of which about three fourth is contained in the plasma and the rest is in the erythrocytes, which make up nearly half of the blood volume. Once absorbed in blood, fluoride immediately spreads the entire body through blood circulation, with almost the entire body burden of fluoride being retained in calcium rich areas of bone and teeth where it is incorporated into the crystal lattice as fluoride has an enhanced affinity for the calcium phosphate in the bones and teeth. Levels of fluoride that are found in the bone vary with the part of the bone examined and with the age and sex. Bone fluoride is considered to be a indicator of long-term exposure to fluoride. The 1st clinical symptom of fluorosis in an affected area may be mottled teeth in children [3]. In India, the most common cause of fluorosis is fluoridated water derived from deep bore wells even from some shallow zone dug wells. Over half of ground water sources in India have fluoride above WHO recommended level [4].

III. Fluorosis

Types of fluorosis

Depending upon the clinical symptoms, there can be three types of fluorosis. These are:

- Dental Fluorosis
- Skeletal fluorosis
- Non-skeletal fluorosis

3.1. Dental Fluorosis

Dental fluorosis is a health condition caused by a person receiving too much fluoride during tooth development. The critical period of exposure is between 1 and 4 years old although fluorosis can affect people of any age[5][6].In its mild form, fluorosis appears as tiny white streaks or specks that are often unnoticeable. The spots and stains left by fluorosis are permanent and may darken over time.In its most severe form, called mottling of dental enamel, it is characterized by black and brown stains, as well as cracking and pitting of the teeth. Although it is usually the permanent teeth which are affected, occasionally the primary teeth may also be affected [7].

H.T. Dean's fluorosis index, developed in 1942, is presently the universally accepted classification system for dental fluorosis. An individual's fluorosis score is based on the most severe form of fluorosis found on two or more teeth[8].

Table: 2 (Dean's Index)

Classification Criteria	Description of enamel
Normal	Smooth, glossy, pale creamy-white translucent surface
Questionable	A few white flecks or white spots
Very Mild	Small opaque, paper white areas covering less than 25% of the tooth surface
Mild	Opaque white areas covering less than 50% of the tooth surface
Moderate	All tooth surfaces affected; marked wear on biting surfaces; brown stain may be present
Severe	All tooth surfaces affected; discrete or confluent pitting; brown stain present

The severity of dental fluorosis depends on the amount of fluoride exposure, the age of the child, individual response, as well as other factors including nutrition[5]. Although it generally accepted that water fluoridation causes fluorosis, most of these are mild and its effects are not felt immediately[9].Severe cases can be caused by exposure to water that is naturally fluoridated to levels well above the recommended levels, or by exposure to other fluoride sources such as brick tea, tooth paste or pollution from high fluoride coal[10].

The condition is more prevalent in rural areas where drinking water is derived from shallow wells or hand pumps and where the modern methods of purification are away from them. It is also more likely to occur in areas where the drinking water has a fluoride content greater than 1 ppm (part per million), and in children who have a poor intake of calcium. Fluoride consumption can exceed the tolerable upper limit when someone drinks

a lot of fluoride containing water in combination with other fluoride sources, such as swallowing fluoridated toothpaste, consuming food with a high fluoride content, or consuming fluoride supplements. Coal burning can pollute air with fluoride. Indoor air with approximately 60 µg F/m³ and drinking water with 3.6 mg F/L are similarly toxic to developing permanent teeth[11]. Dental fluorosis can be prevented by lowering the amount of fluoride intake to below the tolerable upper limit.

3.2 Skeletal Fluorosis

Skeletal fluorosis is a crippling bone disease caused by excessive consumption of fluoride over a period of time. In advanced cases, skeletal fluorosis causes pain and damage to bones and joints. In order to understand the mechanism of fluoride action on human beings, let us discuss the following path ways.

1. Fluorine enters the body either by ingestion or respiration. In either of the way the exposed tissue is affected at high concentrations of fluoride. Hydrogen fluoride, the most likely compound of fluorine to enter the body, utilizes the exposed tissues in neutralization reactions (acid base reaction).
2. Fluoride ion (F^-) produced in the process then becomes free to pass further into the body, reacting with the concentrated HCl secreted in the stomach and again regenerating the weak acid, HF.
3. This compound is then absorbed by the gastro-intestinal tract and passes into the liver via the portal vein. Due to its high electronegativity, fluorine is the strongest known oxidizer known currently and has the highest standard reduction potential of +2.87V**.** Thus it is immune to phase 1 metabolism in the liver and hence in the form of HF freely passes into the blood stream and is distributed to all tissues including bones.
4. Bones are largely composed of Ca compounds, particularly carbonated hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) or $Ca_5(PO_4)_3(OH)$ .When reacted with HF it forms an insoluble salt, CaF_2. This insoluble salt, CaF_2 is cleared by the body through excretion and as a consequence some of the calcium that would have been part of the bone matrix is washed away. This causes increased bone density with decreased bone strength [12].
   Dimineralision Process :
   $Ca_5(PO_4)_3(OH) + HF = Ca_5(PO_4)_3F + H_2O$ (1)
   $Ca_5(PO_4)_3F = 2Ca_3(PO_4)_2 + CaF_2$ (2)

5. Fluoride poisoning can be treated by the administration of soluble Calcium salt such as gluconate or chloride to produce insoluble CaF_2 and to reverse the demineralization process.
   Mineralisation Process
   $3Ca^{2+} + 2PO_4^{3-} = Ca_3(PO_4)_2$ (3)
   $3Ca_3(PO_4)_2 + CaF_2 = Ca_5(PO_4)_3F$ (4)

Skeletal Fluorosis:A Diagonistic Challenge

As of now, there is no established cure for skeletal fluorosis. As we know prolonged and excessive exposure to fluoride causes the skeletal fluorosis. The disease develops gradually and imperceptibly and its symptoms are often difficult to distinguish from a number of other bone and joint diseases. In initial stages, which is known as "pre-skeletal" fluorosis, a patient may suffer from a variety of problems in the absence of any detectable symptoms, because the symptoms are indistinguishable from common forms of arthritis, such as osteoarthritis and rheumatoid arthritis. Due to the absence of bone changes this pre-skeletal phase of fluorosis is difficult to diagnose [13][14]. Even when bone changes do appear there is every probability that it may be misdiagonised as symptoms of other diseases, including osteoarthritis, renal osteodystrophy, spondylosis, Paget 's disease and osteopetrosis etc.

Varied Individual response to fluorosis

Research shows that individual susceptibility to skeletal fluorosis varies widely across the population, both with respect to the doses and duration of fluoride exposure as well as the skeletal manifestations and symptoms that develop due to the disease .

(i) Some individuals can develop skeletal fluorosis despite having safe levels of fluoride in their bones[15].
(ii) Some individuals receiving the same dose of fluoride can exhibit dramatically different bone responses [16].
(iii) Some individuals with pre-skeletal fluorosis may suffer excruciating pain, while some other individuals with advanced fluorosis may remain absolutely symptom-free [17].

(iv) although it is claimed that fluorosis only develops after 10 or more years of exposure, children as little as 6 months are reported to have developed the disease [18], and some adults have developed the disease as early as 2 to 7 years [19][20].

3.3 Non-Skeletal Fluorosis

This kind of fluorosis is often over looked because of the wrong prevailing notion that fluoride affects only bone and teeth. In this context , the words of the American University Chemistry Professor Dr William Hitzy is worth mentioning wherein he says that "it would be a biological miracle if fluoride did not cause other harm prior to producing the end stage form of toxicity like dental fluorosis ans skeletal fluorosis".It is found that fluoride can cause arthritic symptoms and bone fracture well before the appearance of the dreaded fluorosis and it affects many other soft tissues like the kidney, the brain,the pineal gland, the thyroid gland, the arteries, the cardio vascular system, the reproductive system etc other than the teeth and bone. Attempts have been made to highlight the recent advances in the field of non-skeletal fluorosis research.

3.3.1 Fluoride and Diabetes

Diabetes is of two types. Diabetes mellitus and Diabetes insipidus.The former is a potentially life-threatening disease, in which the body fails to properly regulate blood sugar levels. Insulin, a hormone secreted by the beta cells of Islets of Langerhans in the pancreas, is responsible for maintaining appropriate levels of glucose in the blood. It enables the body's cells to absorb glucose from the blood and either use it as an energy source or store it as glycogen. Fluoride has been shown to increase blood glucose levels and impair glucose tolerance, most probably by inhibiting insulin secretion.

Diabetes mellitus(Hyperglycemia)

When carbohydrates taken in our food are digested, glucose level in the blood increases. In case of diabetes mellitus the body is not able to regulate the amount of glucose in the blood and there is elevated blood sugar. The condition of chronic elevated blood sugar is called **hyperglycemia**, a disease that can lead to serious complications like damage to the kidneys, brain and nervous system, cardiovascular system, retina, legs and feet, etc. Human and animal studies have found that excessive fluoride consumption leads to increased blood fluoride levels, with the consequent increase in blood glucose levels.

Blood glucose levels in diabetics are not properly regulated, either because the pancreas does not produce adequate amounts of insulin (i.e., type 1 diabetes mellitus), or because the body's cells have become less responsive to insulin that is produced ("insulin resistance"; i.e., type 2 diabetes mellitus). Studies on both animals and humans have revealed a transient inhibition of insulin secretion following fluoride ingestion, resulting in hyperglycemia. Fluoride may also lead to increased insulin resistance, or decreased insulin sensitivity, thus contributing to glucose intolerance. As a diabetics show polyuria (frequent urination), polyphagia (excessive hunger) and polydispia (excessive thirst) syndromes, they drink more water on an average than nondiabetics, and in the process consume more fluoride on a daily basis from water and other beverages. Furthermore, research has shown that diabetics have a reduced capacity to excrecate fluoride from the body, [21], which may be a result of the kidney damage that accompanies diabetes. In another review it is revealed that diabetes people with kidney problems also have polydipsia-polyurea syndrome that results in increased intake of fluoride and also more-than-normal retention of the fluoride dosage[22]**.**Due to increased intake and retention of fluoride the diabetics are at enhanced risk of fluoride-related toxicity.

Diabetes Insipidus(water diabetes)

This is caused by deficiency of ADH(anti diuretic hormone also called Vasopressin) in which urination is frequent and copious , resulting in loss of water from the body .The patient feels thirsty and drinks excessive amounts of water and in the process consume more fluoride . Researchers have observed moderate and severe dental fluorosis in people with hereditary diabetes insipidus—a result of drinking "optimally" fluoridated water during tooth development.

3.3.2 Fluoride and Kidney

The kidney helps prevent the build-up of toxic fluoride levels in the body by excreting fluoride through urine. When kidney does not function properly, the risk of fluoride toxicity increases. Because the kidney is exposed to higher concentrations of fluoride than all other soft tissues (with the possible exception of the bladder and pineal gland), excess fluoride exposure contributes to kidney damage, thus initiating a "vicious cycle" where the damaged kidneys increase the retention of fluoride, causing in turn further damage to the kidney, bone, and other organs.

In animals, kidney damage has been reported at levels as low as 1 ppm if the animals consume fluoridated water for long periods of time. In humans, elevated rates of kidney damage are frequently encountered among populations with skeletal fluorosis. Individuals with advanced kidney disease are known to have a very high susceptibility to fluoride toxicity since their bones and other tissues accumulate fluoride at levels far higher than healthy individuals. This fluoride build-up places kidney patients at a quite enhanced risk of skeletal fluorosis. Fluoride intake can also contribute to and compound the complex bone disease renal

osteodsystrophy, as well as the tooth staining and disfigurations that many people with advanced kidney disease suffer. Children with kidney disease are at the receiving end for dental fluorosis.

"Because people with kidney disease have an impaired ability to excrete fluoride, they accumulate higher levels of fluoride in their bone than healthy individuals. Because of this, kidney patients bear the brunt of fluoride toxicity at doses well below those that cause harm in others. Thus those with advanced kidney disease, have a heightened vulnerability to fluoride" **(Dr. Helmut Schiffl, 2008).**

3.3.3 Fluoride and Cancer

Recent studies indicate that fluoride is a mutagen i.e. a compound causing genetic damage and hence is likely to contribute to the development of different types of cancer.

Fluoride & Osteosarcoma (Bone Cancer)

Osteosarcoma is a rare, but deadly, form of cancer that strikes primarily during the teenage years. Study by Harvard scientists shows that boys exposed to fluoridated water during the mid-childhood growth spurt have a significantly elevated risk of developing osteosarcoma during adolescence than the girls. [23].

Excess fluoride may be correlated to osteosarcoma on the following grounds:
(i)Bone is the principal site of fluoride accumulation, especially in the formative stage i.e. during early childhood;
(ii)Fluoride is a mutagen when present at sufficient concentrations;
(iii)Fluoride has the ability to stimulate osteoblasts (the proliferation of bone-forming cells) and this increases the risk of dividing some of the cells to become malignant [24].

Fluoride & Bladder/Lung Cancer

Apart from osteosarcoma, exposure of workers to airborne fluoride also contributes to both bladder and lung cancer.Workers exposed to high fluoride without any other carcinogen have also been found to have bladder and lung cancer. Thus it is concluded that fluoride is considered as a possible cause of bladder cancer and a contributory cause of primary lung cancer [25].

3.3.4 Fluoride and Mental Efficiency

Fluoride has the ability to damage the brain. In this context, Fluoride can be grouped with lead, mercury, and other poisons that cause chemical brain drain. Recent studies on the subject have found that
(i)Prolonged exposure to varying levels of fluoride can damage the brain, particularly when coupled with an iodine deficiency, or aluminum excess; persons with moderately high fluoride exposure have reduced intelligence and impaired foetal brain development.
(ii)Animals and humans ingested with excess fluoride have an impaired capacity to learn and/or remember and also have neurobehavioral deficits ;
(iii)Fluoride exposure of women during pregnancy can have damaging effect on the brain of the offspring.
(iv)Fluoride exposure is also associated with reduced IQ in children [80].

3.3.5 Fluoride and Bone Fracture

It is needles to reiterate that high doses of fluoride have damaging effect on the bone tissue. People exposed to excess fluoride are amenable to bone fractures. Researches on human and animal show increased fracture rates with reduced bone strength in communities exposed to high fluoride . Although people receiving fluoride doses in the range of 0.7-1.2 mg/L are not prone to bone fracture individuals in fluoridated communities with kidney disease suffer from fragile bones as a result of their overall fluoride intake. However this finding is not universal and even people exposed to lower levels of fluoride for much longer periods of time are not free from the menace .It is seen that fluoride levels in drinking water that are still considered safe by the WHO also reduce the density of cortical bone and increase the bone fracture rate in certain population [13].

3.3.6 Fluoride and Cardiovascular Disease

Cardiovascular disease is the principal cause of morbidity and mortality in the world today. A number of factors contribute to the development of this disease, including genetics, modern lifestyle and different environmental pollutants. Fluoride is known to accumulate in the cardiovascular system leading to increased blood pressure (hypertension), arterial calcifications, arteriosclerosis, myocardial damage and also electrocardiogram abnormalities in both humans and animals chronically exposed to high fluoride. Research has also found that patients with cardiac failure have significantly high levels of fluoride in their blood sample, even more than the kidney patients.

3.3.6.1 Blood Pressure and Hypertension

Individuals with high blood pressure are considered hypertensive and they are prone to diseases like heart stroke, heart attack, heart failure, aortic aneurysms, and peripheral arterial disease. There is a strong corelationship between excessive fluoride in drinking water and increased incidence of hypertension, especially among adult males [26]. A higher incidence of arterial hypertension has also been seen among those occupationally exposed to high fluoride [27]. Animal studies also confirm this corelationship[30].

3.3.6.2 Arterial Calcification

The major change involved with cardiovascular disease is development of atherosclerosis in critical arteries, which is partially characterized by vascular calcification. Increased arterial calcifications have frequently been reported in those with skeletal fluorosis [28]. Fluoride accumulation leads to cellular toxicity, most probably due to calcium accumulation [30]. The aorta has been shown to accumulate more fluoride than possibly any other soft tissue. Similarly animals chronically exposed to fluoride have increased levels of both fluoride and calcium in the aorta [30] and heart [31].

3.3.6.3 Arteriosclerosis

Healthy arteries are flexible and elastic, allowing smooth and efficient transfer of blood and nutrients from the heart to the rest of the body. Arteriosclerosis refers to a hardening of the arteries due to loss of elasticity and increased bone density. This is a slow, but progressive disease that may begin early in life due to damage of the inner layer of the arteries. This damage is caused by a number of factors including high blood pressure, high cholesterol, diabetes and different environmental factors. Recent studies show that those exposed to high fluoride for a long period of time are prone to the risk of suffering from arteriosclerosis.According to Song et al. (1990), "endemic fluorosis might cause aortosclerosis [arteriosclerosis of the aorta], which greatly aggravate the course and range of sclerosis and calcification of the conducting arteries, and which in turn aggravates fluorosis " [32].

3.3.6.4 Electrocardiogram Abnormalities

Higher rates of abnormal ECGs have been observed among the people with skeletal fluorosis compared to normal human beings [33]. Children with dental fluorosis have also been shown to have altered ECGs, including prolonged Q-T interval [34]. Similar findings have been reported by Okushi (1954) and Takamori (1956){[35] to [37]}. Altered ECG readings have also been observed in experimental animals with chronic and subacute exposure to fluoride{ [34][35][38] to[41]}.

3.3.6.5 Myocardial Damage

Structural damage to the heart resulting from fluoride toxicity has been observed in numerous human and animal studies. The general features of this damage include cloudy swelling, vacuolization or vacuolar degeneration, hemorrhages, interstitial edema, fibrous necrosis, dissolution of nuclei, and thickening of the vessel walls in the heart muscle {[37][42]to[45]}.Fluoride-induced oxidative stress and inflammatory response have been demonstrated in humans and experimental animals [46], and are likely responsible for this myocardial cell damage [47].

3.3.6.6 Cardiovascular Disease Increases Blood Fluoride Levels

Patients with heart disease have higher levels of fluoride in their blood. According to one study, cardiac malfunctioning is associated with higher blood fluoride levels than any other disease type in a group of patients in a fluoridated area[48]. Hence, patients with cardiac malfunctioning have higher blood fluoride levels than patients with kidney disease. Thus chronic cardiac failure is a strong a factor for fluoride accumulation in the blood and vice versa [48].

3.3.7 Fluoride and Gastrointestinal Problems

Excess fluoride intake/ingestion causes a range of gastrointestinal symptoms, including nausea, pain, and vomiting. The National Research Council Report (US) in 2006, found that human beings with high levels of fluoride ingestion can suffer from persistent gastric problems. Humans suffering from skeletal fluorosis, for example, have been repeatedly observed to suffer from high rates of gastrointestinal problems and these gastrointestinal symptoms subside when fluoride intake is reduced. Similarly, when high doses of fluoride (18-34 mg/day) have been administered as an experimental drug to treat osteoporosis, gastric disorders are one of the two main side effects consistently observed in the patients. Fluoride has been found to damage gastric mucosa at relatively low doses [24].

3.3.8 Fluoride and Reproductive Behavior

3.3.8.1 Male Fertility

Fluoride affects male infertility as it reduces sperm court, contributes to abnormal sperm quality (e.g., reduced motility and altered morphology) and alteres the levels of sex hormones (e.g., reduced testosterone). Poland researcher Zakrzewska in 2002 and in 2006 has observed that on exposing ram semen to higher level of fluoride results in significant decrease in the motility of spermatoza and the number of intact acrosomes which affect the physiological function of the sperm[49][50]. Similar findings have been reported by the Texas researcher Chubb who found that infusing testis with higher, but still relatively modest, levels of fluoride inhibited the synthesis of testosterone[51] .

3.3.8.2 Fluoride's Effect on Male Reproductive System – Animal Studies

Animal studies on different animals like rats, mice, chickens, and rabbits show that fluoride adversely affects the male reproductive system. These effects include: (1) decreases in testosterone levels; (2) reduced sperm motility; (3) altered sperm morphology; (4) reduced sperm quantity; (5) increased oxidative stress; and (6) reduced capacity to breed{[52]to[57]} .It is suggested that nutritional supplements like protein or anti-oxidants such as vitamin C can significantly prevent these effects.

3.3.8.3 Fluoride's Effect on Male Reproductive System - Human Studies

High fluoride exposure is linked to reduced testosterone and decreased fertility in humans. Studies of human populations by many researchers have reported associations between fluoride exposure and damage to the male reproductive system [58]. High fluoride exposure is associated with reduced male fertility {[59]to[61]} and with reduced male testosterone levels{[62]to[66]}.

3.3.8.4 Fluoride and Earlier Puberty in Girls

In the United States, children are reaching the age of puberty at earlier ages than in the past .This is a rising trend replete with serious health consequences, including a heightened risk for breast cancer. From animal studies it is found that fluoride exposure causes a decrease in the amount of circulating melatonin leading to accelerated sexual maturation in females [67][68].

3.3.9 Fluoride and Pineal Gland

The pineal gland is one of the smallest and most important endocrine glands located in the centre of the brain close to the pituitary gland. In conjunction with the hypothalamus gland, it is responsible for the synthesis and secretion of the hormone melatonin, a hormone that maintains the body's sleep-wake cycle (circadian rhythm), hunger, thirst, regulates the onset of puberty in females, and helps protect the body from cell damage caused by free radicals. According to Jennifer Luke, the British scientist, significantly high level of fluoride is accumulated in the pineal gland [69]. As already discussed high level of fluoride reduces melatonin levels and causes early puberty in girls. [67]. Basing on the observations made by Luke and other researchers it is stated that fluoride is likely to cause decreased melatonin production and also have other effects on normal pineal function, which in turn could contribute to a variety of health disorders in humans[24].

As a soft tissue that is exposed to a high volume of blood flow, the pineal gland is a major site of fluoride accumulation in humans. Pineal gland calcification is of great concern as it happens at a very young age. In fact, the calcified parts of the pineal gland accumulates the highest fluoride concentrations in the human body in the form of calcium phosphate crystals, becomes hardened and loses much of its functionality due to decreased numbers of functioning pinealocytes and reduced melatonin production [67][69]

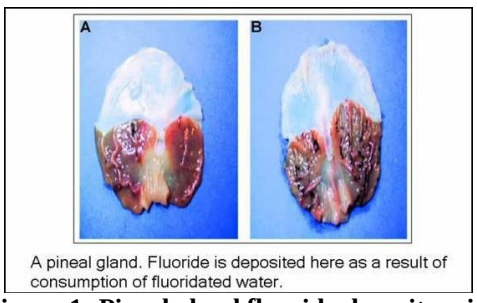

Figure-1: Pineal gland fluoride deposit on it.

3.3.10 Fluoride and Thyroid

The thyroid gland is a bilobed structure situated in front of the neck just below the larynx.It secrets two types of hormones- thyroxine and calcitonin.Thyroxine regulates the basal metabolic rate(the rate of cellular

oxidation resulting in heat production at rest) ,the general growth of the body , ossification of bones, body temperature, mental development and hence plays an important role in human health. Because all metabolically active cells require thyroid hormone for proper functioning, thyroid disruption can have a wide range of effects on virtually every system of the body. Chemicals that interfere with thyroid function also severely affect the human health.

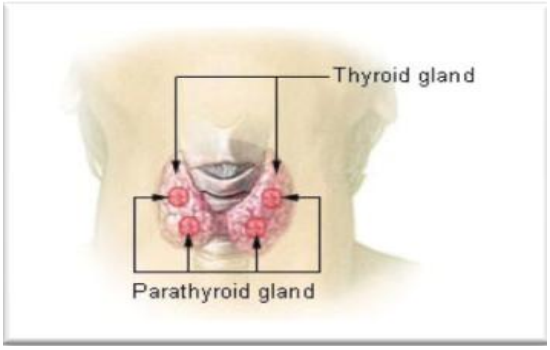

Figure-2: Thyroid and Parathyroid glands

3.3.10.1 Fluoride & Hypothyroidism

A number of studies from China, India, and Russia that have found alterations in thyroid hormones, including reduced T3(3,5,3'-triiodothyronine) and increased TSH(Thyroid Stimulating Hormone), in populations exposed to elevated levels of fluoride in the workplace or in the drinking water. These hormones are required by all metabolically active cells, and their reduced presence can thus produce a range of ill effects, including fatigue, muscle/joint pain, depression, weight gain, menstrual disturbances, impaired fertility, impaired memory, and inability to concentrate{[24][70]to[74]}. Hyperthyroidism also causes different clinical symptoms like weight loss, heat intolerance, rapid heartbeat rate, basal metabolic rate(BMR), irritability, sweating, anxiety, nervousness, tremors etc[1].

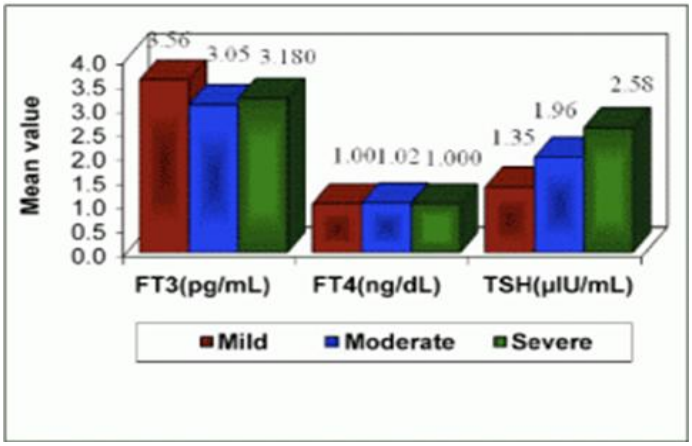

Figure-3: Thyroid Hormone Levels Based on Severity of Dental Fluorosis (Hosur 2012).

3.3.10.2 Fluoride & Goiter

Goiter is an enlargement of the thyroid gland that in some cases can produce visible swelling in the neck. Although it is well known that iodine deficiency is the main cause of goiter, researchers now a days have strong evidence to link excessive fluoride as the a possible cause of goiter. It is seen that human populations having adequate intake of iodine have also goiter problems which can be attributed to fluoride exposure. Thus fluoride's ability to produce goiter is a fact rather than only an assumption [24[75].

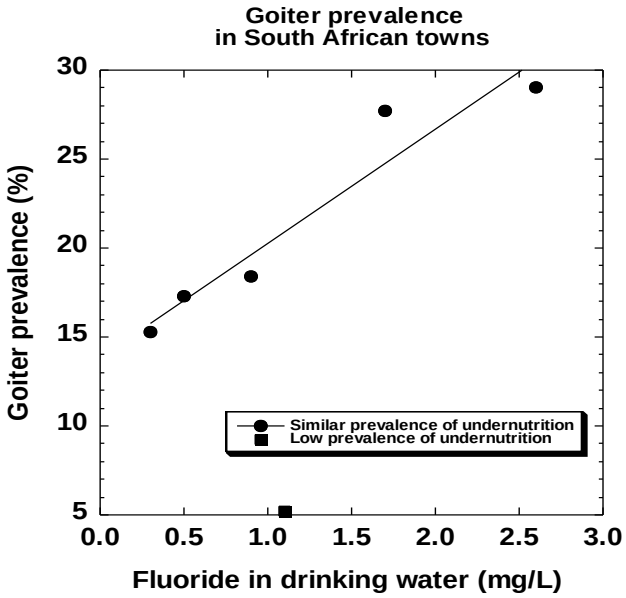

Figure-4: Goiter prevalence in South African Towns(Jooste et al.1999)

Fluoride Impact on Iodine Deficiency

Iodine is the basic building block of the T3 (3,5,3'-triiodothyronine) and T4 (3,5,3',5'-tetraiodothyronine,also called thyroxine) hormones and thus an adequate iodine intake is essential for the proper functioning of the thyroid gland.

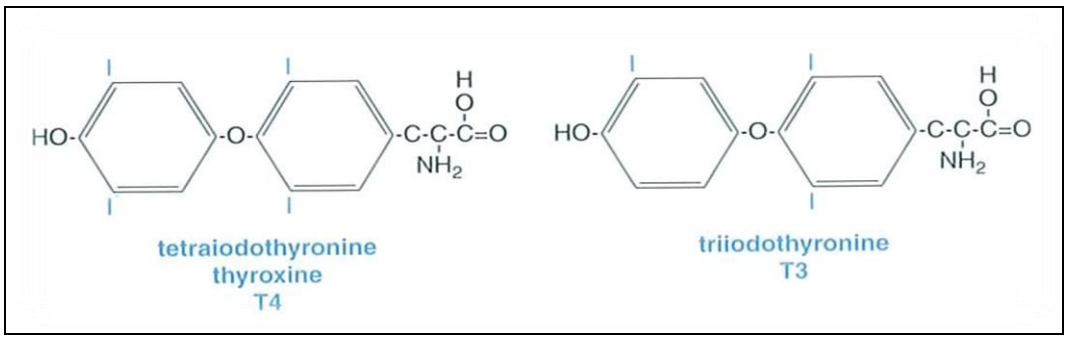

Figure-5: Structure of T3 and T4 Hormone

When iodine intake is inadequate during infancy and early childhood, the child's brain can suffer permanent damage, including mental retardation. It is found from animal and human research that fluoride exposure compounds the impact of iodine deficiency which is the leading cause of mental retardation all over the world{[76]to[84]}**.** An iodine deficiency coupled with high fluoride exposure have more damaging an effect on neurological development than iodine deficiency alone{[77][80]to[83]}. While there is an association between excessive fluoride intake and reduced IQ among children with adequate level iodine intake [85], an iodine deficiency will reduce the threshold level at which fluoride is capable of damaging the brain [80][84] and also reduce the threshold for other forms of fluoride toxicity like dental fluorosis[79].

3.3.11 Fluoride and Parathyroid

Parathyroid glands are two small pair of glands embedded in the back of the thyroid(see Fig-2). Their hormone parathermone promotes movement of calcium ions from the bones to the blood. Excessive secretion of parathormone causes increased mobilization of bone minerals into the blood, softening of bones, rise in concentration of calcium in the plasma and deposition of calcium in kidney tubules and soft tissues. As a result, bone flexibility decreases making the bone more amenable to fractures [18].

Researchers have found elevated parathermone concentrations in some individuals receiving 0.4-0.6 mg/kg/d of fluoride and even in some cases at concentrations as low as 0.15-0.34 mg/kg/d.There is elevated parathermone or clinical secondary hyperparathyroidism in skeletal fluorosis patients, usually with adequate dietary calcium-[18]**.** It is found that children with high fluoride intake suffer from hypocalcaemia(decreased

serum calcium) in comparision to populations with low fluoride intake. However, parathyroid response to fluoride differs significantly from person to person.

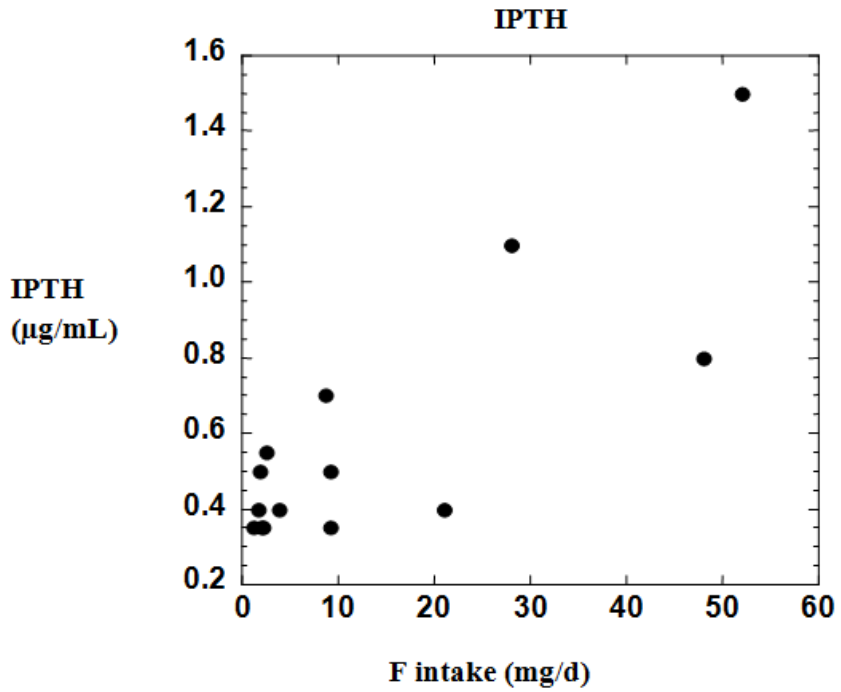

Figure-6: Elevated PTH in Skeletal fluorosis patients (Adopted from Teotia et al 1978)

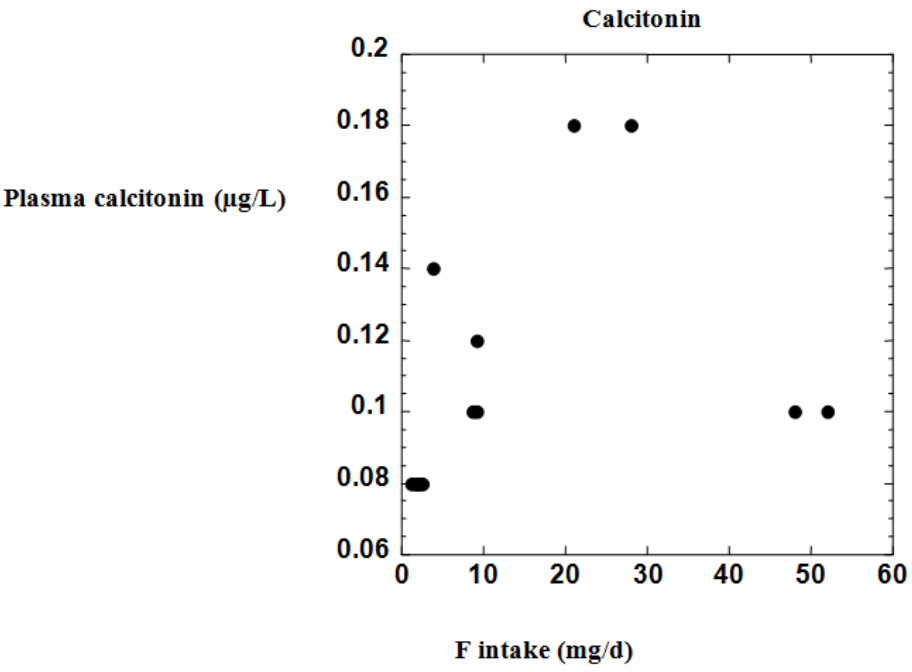

Figure-7:Elevated Calcitonin In Skeletal Fluorosis Patients(Adopted From Teotia Et Al 1978)

3.3.12 Fluoride and Red Blood Corpuscles (RBCs)

Fluoride ingested into the body accumulates on the erythrocyte membrane which, in turn, loses its calcium content and causes formation of echinocytes. The life span of echinocytes is less than the normal life span of RBC and hence early destruction of the RBCs causes anemia in which the soft tissues like ligaments and blood vessels tend to harden and calcify and blood vessels are blocked. Fluoride stimulates granule formation and oxygen consumption in white blood cells (WBC) of the body and reduces the ability of WBCs to properly destroy foreign agents. It also prevents antibody formation in the blood [3]**.**

3.3.13 Fluorosis and Lactation

Maylin and Krook (1982) have studied the effect of fluoride on cattle population and have reported a drop in milk production amongst cattle in the Massena/St. Regis area. They have monitored the milk production in a herd located near an aluminum plant continuously for 20 years. And found that milk production started to decrease from the fifth year of fluoride exposure, by year eight the losses were reduced to the 1% level, and by year 10 to the 19% of the original level. Maylin and Krook (1982) also studied the symptoms in herd of cattle and found that among the cattle herd conception rates were low, retained placentas were very common and the number of abortions increased due to fluoride exposure[86].

IV. Conclusion

Fluorine by its very nature has enhanced affinity towards teeth and bone. Fluorine at low concentration is beneficial for both teeth and bone due to the formation of fluoroapatite which is organic acid resistant and thus strengthens both teeth and bone. Fluoride above the recommended level causes skeletal and dental fluorosis. Fluorine also has the potential to exist as the ion, F^-. This ion is very reactive as a base with organic molecules, resulting in possible reactions with any molecule in the body which can lead to damage at the tissue level , especially the soft tissue[87].Thus it affects the kidney, the brain, the pineal gland, the thyroid gland, the arteries, the cardio vascular system, the reproductive system etc other than the teeth and bone. As of now there is no established treatment for fluorosis. This leaves prevention as the only option to control the menace. Many areas still remain unexplored as to how fluoride affects the vital soft tissues and further research into various aspects is suggested.

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