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Skeletal Fluorosis Due To Chronic Fluoride Intoxication- An Over Review

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Endemic skeletal fluorosis is widely prevalent in India and is major health problem. Epidemiological and experimental studies in the endemic areas suggest the role of temperate climate, hard physical labor, nutritional status, presence of abnormal concentrations of trace elements like strontium, uranium, silica in water supplies, high fluoride levels in food and presence of kidney diseases in development of skeletal fluorosis. 'Skeletal fluorosis' is a condition associated with prolonged accumulation of fluoride resulting in fragile bones having low tensile strength, excessive ossification and joint ankylosis in skeletons. It affects the joints as well as the bones. It is not easily recognizable till advanced stage. In early stages, fluorosis is usually associated only with stiffness, backache and joint pains which may suggest the diagnosis of rheumatoid arthritis, ankylosing spondylitis and osteomalacia. At this stage the radiological findings of skeletal fluorosis may not be evident and therefore most of these cases are either misdiagnosed for other kinds of arthritis or the patients are treated symptomatically for pains of undetermined diagnosis (PUD). So it is necessary to know the sources of fluoride exposure, metabolism of fluoride, pathological changes and clinical manifestation of skeletal fluorosis, diagnostic tools, its management and prevention for the proper understanding of this disease.

Key words- Skeletal fluorosis, Chronic fluoride intoxication, Fluoride, Osteosclerosis, Vit.C,

Introduction

Fluoride has been described as an essential nutrient and recognized to be physiologically essential for the normal development and growth of human beings.[1] To a certain extent (as per WHO; 0.6 ppm) fluoride ingestion is useful for bone and teeth development, but excessive ingestion causes a disease known as Fluorosis. Fluorosis continues to be an endemic problem. More and more areas are being discovered regularly that are affected by fluorosis in different parts of the country.[2] Sixty million Indians are living in about 200 districts of 20 states in endemic areas of fluorosis and are at risk of developing fluorosis. [3] 50-100% districts of various states like Andhra Pradesh, Tamil Nadu, Uttar Pradesh, Gujarat and Rajasthan are affected. [4] The WHO standards and BIS: 10500-1991 permits only 1.5 mg/l as a safe limit of fluoride in drinking water for human consumption. [5][6] In India, fluoride level in ground water varies substantially in different areas. [1] High concentrations of fluoride (>1.5 mg/L) have been reported in the most of the states of India. [7]

It is well established that prolonged use of fluorides as recommended levels does not produce any harmful physiological effects in the humans. However, there are safe limits for fluoride beyond which harmful effects can occur. These effects can be classified as acute and chronic intoxication. [1] Chronic fluoride intoxication has been documented to occur as a result of ingestion of large quantities of fluoride-rich waters, food or both over many years (World Health

Organization, 1970), as well as in occupational exposure in those engaged in aluminium production, magnesium foundries, fluorspar processing, and superphosphate. [8][9] Fluoride toxicity presents with an extraordinary degree of uniformity in its clinical manifestations. [10] Fluorosis is classified into 3 types. They are dental fluorosis, skeletal fluorosis, and non-skeletal fluorosis, out of which dental and skeletal fluorosis is predominantly present in humans. [11] 'Skeletal fluorosis' is a condition associated with prolonged accumulation of fluoride resulting in fragile bones having low tensile strength, excessive ossification and joint ankylosis in skeletons. It affects the joints as well as the bones. It is not easily recognizable till advanced stage. In early stages, fluorosis is usually associated only with stiffness, backache, and joint pains

which may suggest the diagnosis of rheumatoid arthritis, ankylosing spondylitis and osteomalacia. At this stage the radiological findings of skeletal fluorosis may not be evident and therefore most of these cases are either misdiagnosed for other kinds of arthritis or the patients are treated symptomatically for pains of undetermined diagnosis (PUD). [12] In the advanced stages of skeletal fluorosis, the spine may closely resemble the appearance of spondylosis/spondylitis and DISH (Diffuse Idiopathic Skeletal Hyperostosis).[13] so that in its most severe stages it becomes a crippling disability that has a major public health and socio-economic impact, affecting millions of people in various regions of Africa, China and India. So it is necessary to know the sources of fluoride exposure, metabolism of fluoride, pathological changes and clinical manifestation of skeletal fluorosis, diagnostic tools, its management and prevention**.**

Sources of fluoride for human exposure: [2]

Main sources of fluoride for human are Water, Food, Air, Medicament, Cosmetic etc.

Water- Although there are several sources of fluoride intake, it is roughly estimated that 60% of the total intake is through drinking water. This is the most assimilable form of fluoride and hence the most toxic.

Food - The fluoride of food items depends upon the fluoride contents of the soil and water used for irrigation, therefore the fluoride content of the food items may vary from place to place. **Drugs-**Prolonged use of certain drugs has been associated with the chronic adverse effects of fluoride e.g. sodium fluoride for treatment of osteoporosis, Niflumic acid for the treatment of rheumatoid arthritis, use of fluoride mouth rinse (Proflo) to render the tooth stronger.

Air- The use of fluorides in industry leads to occupational exposure e.g. inorganic fluoride compounds are used in the production of aluminum. Fluorides are also released during the manufacture and the use of phosphate fertilizers.

Cosmetics viz. Toothpaste's & Mouth Rinses- Highly significant associations were found between estimated fluoride ingestion from toothpaste and fluorosis. The fluoride content arising from the raw material used for the manufacturing of paste viz. calcium carbonate, talc and chalk have high fluoride arising as a contaminant from raw materials; can be as high as 800-1000 ppm. In the fluoridated brands, there is a deliberate addition of fluoride, which may range form 1000-4000 ppm.

Other-

1. Inorganic fluoride compounds are used in the production of aluminum and use of phosphate

Fertilizers. Apart from the available drinking water supply the bottled mineral water may also be a source of excessive fluoride ingestion. In one study, it is reported that specific bottled waters contained: Significant concentrations of fluoride not reported by the producer. It is therefore concluded, that a sanitary regulatory system for the control of the level of fluoride in the bottled mineral waters marketed is necessary. [14]

Metabolism of fluorides-

The overall metabolism of fluoride can be divided into 3 steps: absorption, distribution, and excretion.

Absorption – Mainly fluoride is absorbed and enters the body through lungs or the gastrointestinal tract. After ingestion of fluoride, such as drinking a glass of optimally fluoridated water, the majority of the fluoride is absorbed from the stomach and small intestine into blood stream. [15] Plasma is the central compartment where the ions pass before being distributed and eliminated. [16] This causes a short term increase of fluoride levels in the blood. The fluoride levels increase quickly and reach a peak concentration within 20-60 min.The concentrations decline rapidly, usually within 3-6 hours following the peak levels, due to the uptake of fluoride by hard tissue and efficient removal of fluoride by the kidneys. [17]

Distribution of fluoride in soft tissues and calcified tissues- Fluoride is distributed from plasma to all tissues and organs. (T/P)Tissue-water-to plasma- water ratio is the index for understanding tissue distribution. Insulin is used as an extracellular marker. T/P of Insulin is 0.2-0.4. Therefore, an agent with T/P higher than 0.4 means that it can penetrate cells. If T/P >1, that agent can accumulate in the tissue. In most organs, such as in liver, lung, heart, salivary gland, T/P ratio of fluoride is 0.4-0.9. This range means that fluoride is able to penetrate cells. (T/P higher than Insulin which is an extracellular marker) but fluoride is not accumulated intracellularly as T/P is less than 1. Some exceptions where fluoride cannot penetrate into brain (blood-brain barrier) and adipose tissues in which T/P ratio of fluoride is 0.08 & 0.11 respectively. T/P ratio of fluoride in kidney is 4.16. This value does not indicate accumulation but is related to the excretion of fluoride by kidney. [16] Approximately 90% of the fluoride retained in the body is deposited in the skeleton

and teeth (calcified tissue). Fluoride exists in both ionic and bound forms in plasma, with the bound form being present in larger quantity.[1] Fluoride in calcified tissues is not irreversibly bound that means, it may be released during normal remodeling of bone.[16] In soft tissues, fluoride has a steady state distribution between the intracellular and extracellular fluids. When the plasma level of fluoride is rising or falling, there is a parallel change in the intracellular fluids. The biological half-life of bound fluoride is several years.

Excretion of fluoride -Roughly 50% of the absorbed fluoride is excreted in the urine during the following 24 hours. Most of the remaining 50% will become associated with calcified tissue. In children less than three years of age only about 50% of total absorbed amount is excreted, but in Adults and children over 3 years - about 90% is excreted.[2] Fluoride also passes through the placenta and also appears in low concentrations in saliva, sweat, and milk.[16]

Pathology of skeletal fluorosis

Skeletal fluorosis results from the ingestion of excessive amounts of fluoride. There is no fixed toxic level of fluoride, since the development of fluorosis depends upon environmental factors. Intoxication can result from acute doses, but more commonly the condition is chronic due to prolonged intake of high levels of fluoride (above 0.7 ppm in some places)[18] Fluoride's actions on bone appear to be mediated at several levels. Fluoride can directly interact with the bone mineral matrix physicochemically.The absorbed fluoride is carried to the bone, where it can replace hydroxyl in the bone hydroxyapatite, creating fluoroapatite. This occurs most rapidly in the trabecular portion of the bone (spongy bone / cancellous bone). Fluorapatite is more stable and resistant to acid dissolution than is hydroxyapatite Fluoride also delays mineralization and is capable of altering bone crystal structure. Fluoride can act on osteoblasts and osteoclasts *in vivo* and *in vitro*. In trabecular bone, fluoride results in an increase in bone volume and trabecular thickness without a concomitant increase in trabecular connectivity. It is this lack of trabecular connectivity that reduces bone quality despite the increase in bone mass. The abnormal bone has an increased density. The absorbed fluoride also stimulates the formation of new irregular bone at the sites of tendon and ligament insertions, resulting in gradual ossification of soft tissues. In the presence of adequate dietary calcium, the main picture is of osteosclerosis; however, in cases where dietary calcium is inadequate, the absorbed fluoride may result in secondary hyperparathyroidism, leading to bone loss, so that bone density may include areas of both sclerosis and porosis. This osteoporotic type of skeletal fluorosis occurs in children and younger adults, particularly in areas with extremely high levels of fluoride in the water. [19]

The factors that may predispose to the development of endemic skeletal fluorosis include: [9]

1. High fluoride intake through water and food,
2. Continued exposure to fluoride,
3. Strenuous manual physical activity and high atmospheric temperature (115-116 f) during summer (both factors likely to lead to high water intake).
4. Poor nutrition, deficient in calories and Vit C.
5. Impaired renal function (diseased kidneys cannot handle fluoride excretion leading to fluoride toxicity and development of skeletal fluorosis even while consuming low levels of fluoride in drinking water supplies).
6. Abnormal concentrations of certain trace elements like strontium, silica, uranium, calcium, magnesium etc in high concentration in water and food could influence fluoride toxicity, some beneficial and others detrimental

Clinical Manifestations [2] [10] [13] [20]

Skeletal fluorosis is a specific form of skeletal disease which follows the absorption of excessive amounts of fluoride for prolonged periods of time. The arthritic symptoms of skeletal fluorosis can occur before the onset of bone changes detectable by x-ray, thereby making the early stages of fluorosis difficult to differentiate from arthritis and other similar arthritic diseases. Osteosclerosis, ligament calcifications and exostoses are the outstanding findings; mottled dental enamel may be seen if the period of absorption includes the first 8 years of life when the enamel of the permanent teeth is being formed. In some instances areas of osteoporosis, osteomalacia, or osteopenia also are seen. Headache, weakness, Vague, diffuse aches,

paraesthesia in limbs and trunk, stiffness of multiple joints with decreased range of motion are common initial symptoms.

Multiple joint pains mostly occur in the feet, knees, heel and back region. As the disease progresses all bones eventually become sclerotic; there seems to be a predilection, however, for flat bones, such as those of the pelvis and jaw, and especially the lumbar vertebral system to show the first detectable changes. In severe cases, exostoses become evident on the long bones, and on the lower edges of the vertebrae. Eventually the vertebrae fuse together, the spinal ligaments become calcified at their points of attachment and the typical rigid spinal column ensues which is called *poker back spine* which is also found in ankylosing spondylitis. Ankylosis of the costovertebral and costosternal joints may occur, with consequent ‘‘freezing’’ of the chest cavity in an aspirated position. Men suffer more than women. Skeletal fluorosis becomes crippling between 30-50 years of age in endemic areas. New comers to endemic area develop symptoms within 4 years of arrival.

Clinical Grading of skeletal Fluorosis-[21]

Grade I: Mild - generalized bone and joint pain.
Grade II: Moderate - generalized bone and joint pain, stiffness and rigidity, restricted movements at spine and joints.
Grade III: Severe - symptoms of moderate grading with deformities of spine and limbs, Knock knees, crippled or bedridden state.

Diagnostic tools for detecting Skeletal Fluorosis

There are so many diagnostic tools/investigations available for the proper diagnosis of skeletal fluorosis, like simple methods such as evaluation of water and blood fluoride levels, observation of clinical signs and symptoms to the par excellent tools like radiological and haematological evaluation, MRI etc.

Evaluation of high fluoride contents of the drinking water- Conc. of fluoride in drinking water can be evaluated by using ion selective electrode method using an ion-ppt meter.

Endemicity of the fluorosis in the area-High concentrations of Fluoride (>1.5 mg/l) have been reported in the states of Haryana, Delhi, Rajasthan, Karnataka, Uttar Pradesh, Maharashtra, Gujarat, Madhya Pradesh, Andhra Pradesh, Tamil Nadu, Kerala, Jammu and Kashmir, Punjab, Orissa, Himachal Pradesh, and Bihar. So it is essential to evaluate fluorosis prone areas. [1]

Evaluation of clinical manifestations of skeletal fluorosis in the population: Symptoms of skeletal fluorosis in early stages can be misdiagnosed with other arthritic disease like ankylosing spondylitis. So proper understanding and observation of symptoms of skeletal fluorosis is essential.

Clinical examination: [2] Examination of teeth and three simple diagnostic tests should be used in clinical practice for getting an idea of diagnosis of skeletal fluorosis.

a. The individual is made to bend and touch the toes without bending the knees. If there is pain or stiffness in the backbone, hip and joints, this exercise will not be possible.
b. The individual is made to touch the chest with the chin. If there is pain or stiffness in the neck, this exercise will not be possible.
c. The individual is made to stretch the arms sideways, fold the arm and try to touch the back of the head. If there is pain or stiffness in the shoulder joint and backbone, this exercise will not be possible.

Urinary and bone fluoride level

Urinary fluoride levels are the best indications of fluoride intake. Since fluoride excretion is not constant throughout the day, 24-h samples of urine are more reliable than random or morning samples.[22] [23]In normal individuals urinary fluorides fluctuates widely between 0.1 to 2.0 PPM (average 0.4 PPM) when the fluoride content of drinking water is 0.3 PPM. There is a linear relation between urinary fluoride levels and fluoride intake. [23]

Bone fluoride content- measures the extent of bone fluoride retention and is useful complement of bone histological studies for the diagnosis of skeletal fluorosis and can be used for the management of fluoride treatment of osteoporosis. In skeletal fluorosis fluoride content varies between 6000 and 8400 PPM in bone ash. Normal between 500 and 1000 PPM or mg/kg. [9]

Radionuclide bone scan- Technetium labeled methylene diphophonate (99mTc-MDF) bone scanning measures skeletal metabolism and in skeletal fluorosis shows mostly a super scan appearance and in some cases joint abnormalities. Increased tracer activity between the forearm bones and diffuse linear tracer activity along the ligamentous attachments may be seen. Concentration of tracer may be noted in the joints such as sacro-iliac, anterior iliac spine where inguinal ligament is attached. [27]

Hematological findings- Normal blood fluoride levels in non endemic regions varied between 0.002 and 0.008 mg/100ml and in endemic regions the levels range between 0.02 and 0.15 mg/100 ml whereas in patients with skeletal fluorosis the levels varied between 0.02 and 0.19 mg/100 ml. [9] The echinocytes are found in large numbers depending upon the extent of fluoride poisoning and duration of exposure to fluoride. It is now known that when fluoride is ingested, it is accumulated on the erythrocyte membrane, which is deficient in calcium content, is pliable and is thrown into folds. The RBCs attain the shape of an amoeba with pseudopodia –like folds projecting in different directions, which are termed as echinocytes. Although the normal RBCs in humans have a life span of 120-130 days, the echinocytes undergo phagocytosis (eaten-up by macrophages) and are eliminated from circulations. This means that RBCs in individuals exposed to fluoride poisoning would not live the entire life span, but are likely to be eliminated as echinocytes. This results in low hemoglobin levels in patients who are chronically ill due to fluoride toxicity. Anaemia and depression sets in. [24] [25]

Radiological findings- In skeletal fluorosis, radiological findings closely parallel the pathological changes. It is difficult to assert that the density of bone is a result of reactive new bone formation and osteoid as a result of fluoride as a response to fluoride intoxication. All that can be said is that the density may be quantitative rather than qualitative owing to increase in mineralization. Bone continues to be formed, but the thickened trabeculae with uncalcified borders are resistant to resorption and so they thicken. In adults, the radiological findings can be categorized into 3 stages: **Grade I: Mild –** there is only osteosclerosis, findings mainly confined to axial skeleton, thickening and coarsening of bone trabeculae, with a corresponding increase in bone density resulting in a ‘‘ground glass’’ appearance on X-rays **Grade II: Moderate** - osteosclerosis, thick primary trabeculae merge with sclerotic secondary trabeculae to make bone homogenously dense. Bone contours become uneven, periosteal bone formation, calcification of interosseous membrane, ligaments (paraspinous, sacrospinous and sacrotuberous ligaments), capsules, muscular attachments, tendons. **Grade III: Severe** - findings as in moderate with exostoses, osteophytosis and associated metabolic bone disease. Axial skeletal bones demonstrate the typical radiological features; calcification is marked at the insertion of muscles and tendons. There can be overlap of radiological features. [9][21]

Imaging- computer tomography (CT) is the best imaging modality for visualization of bone pathology and provides more details than plain skiagrams. [26] CT visualizes better the direction of the osteophytes, a finding which may help in surgical planning. Spinal canal and root canal stenosis is also better appreciated with CT scan. The calcified ligaments are visualized with much more clarity and earlier than by roentgenology, so are the indentions of the epidural space and the alterations in the spinal canal. By reconstruction, CT provides exact dimensions of the ossified intraspinal ligaments such as posterior longitudinal ligaments and yellow ligaments. [27]

Magnetic resonance imaging (MRI) being noninvasive obviates the difficulties in performing myelography and also delineates soft tissue structures and changes in the spinal cord. It also demonstrates associated abnormalities like pseudomeningocoele, it is worthwhile to image the entire spine, which may

demonstrate incidental and interesting pathological lesions peculiar to fluorosis. Fluorotic vertebrae are hypointense in both T1 and T2 weighted images.[27]

Differential diagnoses

In the early stages of skeletal fluorosis patients complain of arthritic symptoms, which have to be differentiated from those caused by such diseases as rheumatoid arthritis and ankylosing spondylitis. For early diagnosis of skeletal fluorosis, microradiographic techniques are more helpful than conventional skiagrams. In doubtful cases a bone biopsy (though tedious) for estimation of fluoride content provides conclusive evidence. In later stages skeletal fluorosis is marked by restriction of spine movements and hence can be easily diagnosed. In the case of children residing in endemic regions these symptoms need to be differentiated from rickets, and sometimes from renal osteodystrophies, including congenital malformations. In all such cases urinary and serum levels of fluoride and radiographs of skeleton will clinch the diagnosis. When sclerosis of the vertebral column is not marked, calcification of the interosseous membranes in the fore arm clearly indicates the diagnosis of fluorosis, on radiography. [2]

Treatment and Prevention

There is a crying need to overcome the problem of fluorosis. The best approach to tackle this public health menace will be prevention since no cure is possible once the disease sets in.

Health Education

A. Creating disease awareness

Creating awareness about the disease should be in form of graphic presentation of the final consequences of the disease to the extent possible. If required live presentation of the patients, who are suffering from the severe form of the disease, in areas where the gravity of problem has not reached to that extent. It may be of use, to demonstrate the most severe extent of the disease and to motivate them to use the preventive or therapeutic measures. [2]

B. Creating awareness about the sources of the fluoride

The creation of awareness will help in implementing the need based preventive measures in the affected community.

C. Treatment of the disease

Patients with skeletal fluorosis, when kept off fluoride intake, register a negative fluoride balance while continuing to excrete large amounts of fluorides for years. It is obvious that excretion of fluorides metabolized from the skeleton through urine and feces is a very slow and prolonged process lasting for many months to even years.[9] Studies, both in vitro and in vivo, have been done to study the effect of various drugs on the binding of fluoride and also on the excretion of fluoride. In vitro studies have demonstrated that bone meal, serpentine, dowex, and magnesium compounds could be effective in reducing fluoride content of water. In vivo experiments in animals showed that Vitamins C and D, and, salts of Calcium, Magnesium or Aluminum could reduce fluoride absorption and also increased its excretion from the body so these were prescribed in an attempt to reverse these effects.[28] Recent studies conducted in Rajasthan under Rajasthan DST sponsored studies indicated that fluorosis could be reversed, in children, by a therapeutic regimen (Calcium, Vitamin C and Vitamin D) which is cheap and easily available.[2] The choice of the reported therapy was logical. The presence of calcium in gut directly affects the absorption of fluoride ions and will also improve serum calcium levels as observed by (Teotia et al53) Vitamin D3 in low doses enhances calcium absorption and retention without causing hypercalcemia and thus directly affects the absorption of fluoride ions. It also inhibits the excessive release of parathyroid hormone thereby preventing excessive activation of osteoblasts thus preventing hyperosteoidosis and osteopenia. Ascorbic acid controls collagen formation, maintains the teeth structure and is also essential for bone formation. These structures are adversely affected by higher fluoride intake. [2] Serpentine was used to increase fluoride excretion in human fluorosis with some success. Serpentine, a naturally occurring mineral, is chemically a magnesium metasilicate and has enormous capacity to absorb fluoride at wide range of pH. There is need to do long term studies to see the effectiveness of these agents in mobilizing fluoride in human fluorosis. Experiments

conducted by marier found a similarity between magnesium deficiency symptoms and those of fluoride intoxication, which made them suggest that higher intake of magnesium, might prove beneficial in endemic skeletal fluorosis. [28] In recent animal experiments, aqueous extracts of *Tamarandus indica* fruit pulp and *Moringa olifera* seeds had some potential to reduce fluoride accumulation and resultant cortical thinning in long bones. So these two plants have some potential to mitigate toxic effects of excess fluoride. Previously extracts of *T. indica* fruit pulp and *M. olifera* seeds have been found to enhance the urinary fluoride excretion which conquered the effects of these two drugs in mitigation the toxic effect of fluoride.[29]

Prevention

a. Providing defluoridated water for drinking purpose

Methods of defluoridation recommended so far are aimed at bringing the fluoride levels to the WHO standards. [2] Defluoridation plants based on Nalgonda method of lime and alum and domestic units were based on filtration of fluoride-rich water with PAC granules, which are activated alumina. Aluminium has been incriminated in the causation of two neurodegenerative diseases Parkinsonism and Amyotrophic lateral sclerosis. Defluoridation methods increase aluminium levels of filtered water and hence these methods are not preferred by WHO. [9] So it is necessary to find out other conventional methods of defluoridation.

b. Changing the dietary habits

Defluoridation of drinking water alone shall not bring the fluoride level to a safe limit. It would be necessary to overcome the toxic effects of the remaining fluoride ingested through other source. This can be done by effecting minor changes in the diet and dietary habits of the population compatible with their social system and available resources. The main aim should be to restrict use of fluoride rich food, cosmetics.[2] Use of food having adequate calcium, vitamin C and proteins should be used in diet to reduce the toxicity of fluoride.[9]

Conclusion- There are so many arthopathies we treated routinely in our clinical practice. Skeletal fluorosis is disease which primarily affects the bones, joints, and ligaments having clinical manifestations as same as that of other orthopathies like Ankylosis spondylitis, osteoporsosis etc. in its early stages. As the prevalence of endemic skeletal fluorosis is high in India, it is necessary to understand to the sources of fluoride intoxication other than fluorinated water, its clinical manifestations, diagnostic tools, preventation and treatment for the proper diagnosis of skeletal fluorosis. So that patient will keep away from unintentional misdiagnosis for other kinds of arthritis rather than skeletal fluorosis.

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