CHAPTER - I

INTRODUCTION
1. INTRODUCTION

Fluorine (Latin: fluere, meaning "to flow"), is the chemical element with the symbol F and atomic number 9. Elemental fluorine was isolated by Henri Moissan in 1886. Atomic fluorine is univalent and is the most chemically reactive due to the highest electronegativity of 3.98 (Pauling scale) of all the elements. In its elementally isolated (pure) form, fluorine is a poisonous, pale, yellow-green gas with chemical formula F₂. Like other halogens, molecular fluorine is highly dangerous and it can cause severe chemical burns on contact with skin. In aqueous solution, fluorine commonly occurs as the fluoride ion -F⁻, although hydrogen fluoride is such a strong acid that substantial amounts of it are present in any water solution of fluoride at near neutral pH (David, 2006).

Pure fluorine (F₂) is a corrosive pale yellow or brown gas that is a powerful oxidizing agent. It is the most reactive and electronegative of all the elements, readily forms compounds with most other elements and often substituted for hydrogen. Fluorine even combines with the noble gases, krypton, xenon, and radon. Even in dark and cool conditions, fluorine reacts explosively with hydrogen. It is reactive to glass, metals and even water as well as other substances. It is far too reactive to be found in elemental form and has such an affinity for most elements, including silicon, that it can neither be prepared nor be kept in ordinary glass vessels. Instead, it must be kept in specialized quartz tubes lined with a very thin layer of fluorocarbons. In moist air, it reacts with water to form dangerous hydrofluoric acid. Other forms are fluoro-complexes, such as (FeF₄⁻), or H₂F⁻. Fluorine is also part of certain drug molecules to resist detoxification in the liver by the cytochrome P₄₅₀ oxidase because the strong C-F bonds are not easily broken. This is to ensure that orally administered medications are not inactivated before reaching the blood stream.

Fluoride is the ionic form of fluorine. Fluorides are organic and inorganic compounds containing the element fluorine. As a halogen, fluorine forms a monovalent ion (-1 charge). Fluoride forms a binary compound with another element or radical. Examples of fluoride compounds include hydrofluoric acid (HF), sodium (NaF) and calcium fluoride (CaF₂), and uranium hexafluoride (UF₆). Fluorine compounds with metals are among the most stable of salts. Fluoride
Compounds, usually calcium fluoride, are naturally found in low concentration in drinking water and some hot drinks, such as tea. The ocean itself has an average concentration of 1.3 ppm.

Fluoride in a concentrated form is used as a prescription drug. Fluoride containing compounds such as sodium fluoride, calcium fluoride, and sodium monofluorophosphate are commonly added to toothpaste, drinking water, prescribed treatments and other commercially available oral hygiene products because fluoride strengthens the tooth enamel. Originally, sodium fluoride was used to fluoridate water. However, hexafluorosilicic acid (H₂SiF₆) and its salt sodium hexafluorosilicate (Na₂SiF₆) are more commonly used, especially in the countries like United States.

Both elemental fluorine and fluoride ions are highly toxic and must be handled with great care and any contact with skin and eyes should be strictly avoided. Contact of exposed skin with hydrogen fluoride solutions poses one of the most extreme and insidious industrial threats — one which is exacerbated by the fact that hydrogen fluoride damages nerves in such a way as to make such burns initially painless. The hydrogen fluoride molecule is capable of rapidly migrating through lipid layers of cells which would ordinarily stop an ionized acid and the burns are typically deep. Hydrogen fluoride may react with calcium permanently damaging the bone. More seriously, reaction with the body's calcium can cause cardiac arrhythmias followed by cardiac arrest brought on by sudden chemical changes within the body. These cannot always be prevented with local or intravenous injection of calcium salts. If the patient survives, hydrogen fluoride burns typically produce open wounds of an especially slow-healing nature.

Fluorosis is a para metabolic bone disease caused due to environmental toxin, fluoride. It is a major public health problem in many states of India. It is caused by excessive ingestion of fluoride and is associated with calcified tissues. The high affinity of fluoride for calcium ions leads to formation of calcium fluorapatite and deposits in the tissue matrix resulting in functional derangement (Susheela, 1993).
Endemic fluorosis is a disease caused by ingestion of a large amount of fluoride through water and food and it continues to be a challenging National health problem resulting from long-term consumption of water with high fluoride levels. The concentration of fluoride in drinking water varies from one geographical region to another. The water fluoride levels ranges from 0.5 to 25.0 ppm in different parts of our country. This amount of fluoride is high compared to WHO, which defines water fluoride >1.0 ppm as endemic for fluorosis (WHO, 1994; Sangh et al., 1996). The disease is prevalent in fifteen states of India (Gopalakrishna et al., 1999). Twenty five million people of 150 districts in India are exposed to the risk of fluorosis (RGNDWM, 1993). Regular excessive ingestion of fluoride results in accumulation of fluoride in the body. The major part of accumulation is in the bone itself. Fluoride is a potent toxic ion, which can alter accretion and absorption of bone tissue and affect bone metabolism. Fluoride is rapidly removed from the plasma by mineralized tissue in exchange with other anions such as hydroxyl ion, citrate, and carbonate in contrast to soft tissue, which does not accumulate fluoride.

In an adult, over 95 per cent of total body fluoride is accounted for by that found in bones and teeth. The most prominent features of fluorosis are dental and skeletal abnormality. The characteristic feature of dental fluorosis is dental mottling and teeth exhibit the first sign of chronic fluoride toxicity. The skeletal changes are caused by accumulation of excessively ingested fluoride, which has been incorporated into the hydroxyapatite crystals leading to formation of fluoroapatites. The newly formed bone with fluorapatite structure is poor in crystalline and matrix strength, which leads to the spectrum of changes of skeletal fluorosis namely osteosclerosis, osteoporosis and fracture of bone. Impaired bone collagen synthesis and increased avidity for calcium in the growing bones in children are features of chronic fluoride toxicity, which leads to bowing of legs termed as genuvalgum (Krishnamachari, 1986; Susheela, 1993). The clinical presentation of the disease is modified by nutritional status, age, dietary habits, urinary pH etc.

Shortt et al., (1937) first reported that chronic fluoride toxicity leading to the specific crippling disease in Podili and Darsi villages of Prakasam district of Andhra Pradesh, India.
Apart from drinking water, there could be several other sources from which fluoride is ingested such as foods grown locally which can add on the body's burden of fluoride. Consumption of certain staple foods such as sorghum, bajra and parboiled rice are reported to be associated with higher prevalence of fluorosis (Krishnamachari et al., 1976; Lakshmaiah and Srikantaiah, 1977; Chari et al., 1974). The severity of fluorosis increases with age, which is indicative of accumulation of fluoride in the body with increase in the age. Males show higher severity of dental and skeletal fluorosis than females (Choubisa et al., 1997; Kahama and Kariuki, 1997; Ray et al., 1981; Pushpa Bharathi and Meera Rao, 2003).

Fluoride is a cumulative toxin, which can alter accretion and resorption of bone tissue. It also affects the homeostasis of bone mineral metabolism. The total quantity of ingested fluoride is the single most important factor, which determines the clinical course of the disease, which is characterized by immobilization of joints of the axial skeleton and other major joints of the extremities. A combination of osteosclerosis, osteomalacia and osteoporosis of varying degrees as well as exostosis formation characterizes the bone lesions. In a proportion of cases, secondary hyperparathyroidism is observed with associated characteristical bone changes. Increased metabolic bone turnover, impaired bone collagen synthesis and increased avidity for calcium are features of fluoride toxicity. Alterations in hormones concerned with bone mineral metabolism are seen in fluorosis (Krishnamachari, 1986). Recent studies (Harinarayan et al., 2006) revealed that fluoride intoxication plays an important role in the pathogenesis of fluorotoxic metabolic bone disease, which is a unique osteo-renal syndrome. In vitamin D deficient individuals, cartilage cells of matrix and the osteoid matrix are not calcified when fluoride intoxication occurs (Chatterjee, 1985). Nutritional deficiency of vitamin D suggests that nutritional osteomalacia and rickets co-exist in patients with fluorosis (Misra et al., 1992). Fluorosis has been linked to the combination of excess fluoride, low calcium intake and high PTH levels. The increase in PTH correlated well with excess fluoride ingestion (Dote et al., 2002).

Nutritional factors play a vital role in the bone homeostasis. Increasing dietary calcium intake favors bone mineral accretion during infancy, childhood and adolescence (Parfitt et al., 1982). A close relationship exists between nutritional
factors and the occurrence of fluorosis. Higher levels of molybdenum intake have been shown to influence the severity of the disease (Anasuya Das, 1998). Inadequate intakes of energy, protein, calcium and ascorbic acid in fluorotic children (Moudgil and Srivastava, 1986; Mukta Agrawal and Purva Johri, 1998; Teotia and Teotia, 1994) and in adults (Sangh and Bal, 1998; Chakma et al., 2000) have been associated with the severity of the disease.

The maintenance of proper calcium levels in cells and extracellular fluids is of fundamental importance for many biological processes. Calcium is essential in maintaining bone health and plays an integral role in the homeostasis between blood and bone calcium levels. The functions of calcium in bone include: bone formation and growth, maintenance of bone density, bone strength and structure and preventing osteoporosis. Vitamin D and PTH are the most important regulators of calcium homeostasis. Deficiencies of calcium and vitamin D can cause decreased bone density (osteoporosis), weak bones which can lead to diseases including rickets, stress fractures and osteopenia. Calcium and vitamin D under nutrition can adversely affect the bone mineral metabolism. PTH regulates calcium level in blood and calcium metabolism in the bones. It acts directly on the bone releasing calcium from bones and thus maintaining the plasma calcium level (Swaminathan, 1993). Vitamin D is necessary for the calcification of bone. It also showed that calcium absorptive performance of the gut is a function of 25-OH vitamin D status of an individual (Mithal et al., 1993; Bischoff et al., 2003). When there are low 25-OH vitamin D concentrations, the effective calcium absorption from the gut is reduced (Bischoff et al., 2003; Heaney, 2003). This is further amplified by the low dietary calcium intake.

Studies on the kinetics of calcium metabolism using radioactive $^{44}$Ca showed that there is a simultaneous increase in bone formation as well as resorption in fluorotics. While osteosclerosis, which is a main feature of fluorosis, could be a reflection of higher rate of collagen mineralisation (bone formation), increased plasma hyperparathyroid activity often encountered in endemic fluorosis explains the phenomenon of increased bone resorption (Sriranga Reddy and Narasingarao, 1977).
Studies carried out on fluorosis so far are mostly prevalence studies. Scanty information on fluorotic subjects investigating biochemical, hormonal and radiological aspects including nutritional status are very meager (Krishnamachari and Krishnaswamy, 1973; Moudgil and Srivastava, 1986; Misra et al., 1992; Gupta et al., 1993; Chakma et al., 2000; Shivashankara et al., 2000; Harinarayan et al., 2004 & 2006; Srivastava et al., 1989; Gupta et al., 2001; Mukta Ágarwal and Purva Johri, 1998; Sangh and Bal, 1998; Pushpa Bharathí and Meera Rao, 2003).

In fact, studies involving nutritional status, dietary intake, biochemical and hormonal assessment with a comprehensive approach are lacking. Further, almost all studies showed a combined effect of a wide range of fluoride levels of drinking water, which does not make it clear of the effects of fluoride levels just above the WHO cut off levels and the trends in increasing fluoride levels. With this milieu, the present study is contemplated on the population residing in fluorotic areas with drinking water fluoride content of >1.0 to 2.0 ppm and above.

Objectives:

1. To assess the nutritional status of individuals of different age and sex groups residing in fluorotic and non-fluorotic areas.
2. To assess the bone mineral status of individuals of different age and sex groups affected by fluorosis residing in fluorotic and non-fluorotic areas.
3. To assess the protein status of individuals of different age and sex groups affected by fluorosis residing in fluorotic and non-fluorotic areas.
4. To assess the vitamin D status of individuals of different age and sex groups affected by fluorosis residing in fluorotic and non-fluorotic areas.
5. To study the interaction between fluoride status and other parameters such as bone mineral status, hormonal status, body and nutritional status indices.
6. To take remedial measures based on above results.