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Endemic Chronic Fluoride To ity and Dietary Calcium Deficiency Interaction Syndromes of Metabolic Bone Disease and Deformities in India : Year 2000

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Abstract : Epidemiological studies during 1963-1997 were conducted in 45,725 children exposed to high intake of endemic fluoride in the drinking water since their birth. Children with adequate (dietary calcium > 800 mg/d) and inadequate (dietary calcium < 300 mg/d) calcium nutrition and with comparable intakes of fluoride (mean 9.5 ± 1.9 mg/d) were compared. The toxic effects of fluoride were severe and more complex and the incidence of metabolic bone disease (rickets, osteoporosis. PTH bone disease) and bony leg deformities (genu valgum, genu varum, bowing, rotational and wind-swept) was greater (> 90%) in children with calcium deficiency as compared to < 25% in children with adequate calcium who largely had osteosclerotic form of skeletal fluorosis with minimal secondary hyperparathyroidism.

The syndrome of skeletal fluorosis and associated metabolic bone disease and deformity is a unique clinical entity classified as a variant of osteosclerotic form of skeletal fluorosis. This syndrome chiefly results from the biological impact of excess fluoride, low calcium, high PTH and 1,25 $(OH)_2D_3$ separately and through their interactions on bone structure and metabolism as studied by radiology, bone scanning, bone histomorphometry and relevant metabolic and endocrine laboratory investigations. Metabolically active and vascular bones of children accumulate fluoride at faster and greater rate than adults (at the sites of active growth). In calcium deficient children the toxic effects of fluoride manifest even at marginally high (> 2.5 mg/d) exposures to fluoride. Fluoride toxicity also exaggerates the metabolic effects of calcium deficiency on bone. The findings strongly suggest that children with calcium deficiency rickets reported in the literature should be re-investigated for possible fluoride interactions. Deep bore drinking water supply with fluoride < 0.5 ppm and improvement of calcium nutrition provide 100% protection against the toxic effects of fluoride and are recommended as the cost effective and practical public health measures for the prevention and control of endemic fluorosis. **(Indian J Pediatr 1998; 65 : 371-381)**

Key words : *Fluoride; Calcium deficiency; Metabolic bone disease; Bony leg deformities; Hyperparathyroidism.*

Endemic skeletal fluorosis continues to remain a challenging national health problem. Reports in the literature on skeletal fluorosis in children are sparse and it was, for the first time, reported by Teotia *et al*[1,2] (1969 and 1971). Subsequently, we reported neonatal skeletal fluorosis in babies born to the mothers who had been residing in vil-

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lages affected with endemic fluorosis during their pregnancy[3]. The authors[4,5,6] and several other workers[7,8,9] since then have reported skeletal fluorosis from several states of India, particularly Andhra Pradesh, Karnataka, T.N., Maharashtra, Gujarat Rajasthan, M.P, Punjab, U.P., Haryana, Bihar and W. Bengal.

Our more than three decades of continuing epidemiological studies[10,14] on the prevalence of endemic fluorosis indicate that over 60 million children are afflicted with endemic skeletal fluorosis in India. Considering the inevitable growth of the population and the identification of new villages endemic for fluorosis, we think that by 2000 AD, the total no. of children at risk who may have to be protected against fluorosis may well be around 100 million.

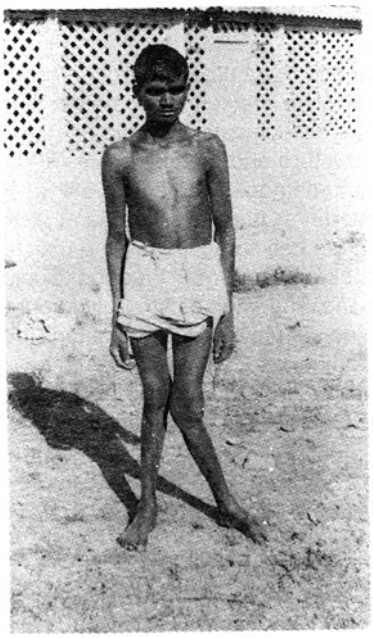

Fig. 1. Syndrome of severe genu valgum and leg rotation deformities caused by fluoride and calcium deficiency interactions in a patient of skeletal fluorosis (16 M).

During our field studies[6,11] our attention was drawn to the high incidence of bone disease and bony leg deformities with clinical invalidism in children exposed to high intake of endemic fluoride in drinking water. Due to variable and unusual clinical features, these children had often been mistaken for rickets, renal osteodystrophy, osteosclerosis and hereditary osteopathies etc.

Comprehensive epidemiological surveys[6, 11, 13, 14] performed during the period

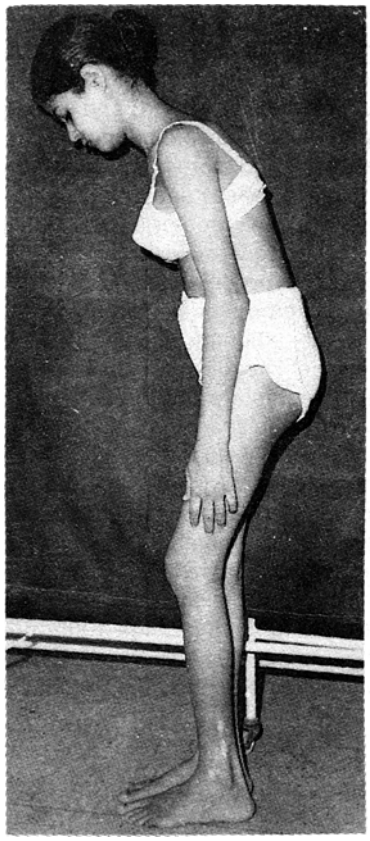

Fig. 2. Patient (15 F) of endemic skeletal fluorosis with stiffness, rigidity and generalised forward flexion deformities at the spine, hips, knees and elbows causing clinical invalidism.

Fig. 3. Clinical picture of the child (8 M) with endemic skeletal fluorosis and bony leg deformities with anterolateral rotation and torsion of legs.

1963-1997 on the prevalence of endemic fluorosis in 0.4004 million children residing in 0.34 million villages of India revealed that 45% of the drinking water sources had high content (1.5-25 PPM) of fluoride in the drinking water.

In this communication we reviewed our extended work on 45,725 children (volunteered for examination) with chronic fluoride toxicity and dietary calcium deficiency interaction syndromes of bone disease and deformities associated with endemic skeletal fluorosis.[6,11,14] All the children have lived in endemic fluorosis affected villages since their birth and consumed water with high (1.5-25 PPM) content of natural fluoride. Groups with adequate (dietary calcium > 800 mg/d) and inadequate (dietary calcium < 300 mg/d) calcium nurition and with comparable ingestion of fluoride (9.5 ± 1.9 mg/d) in drinking water were contrasted.

The incidence and the clinical (figs. 1, 2, 3) and radiological (figs. 4, 5, 6, 7) severity of skeletal fluorosis (Table 1) and metabolic bone disease[15,16] (rickets, osteoporosis, PTH bone disease) and bony leg deformities (genu valgum, genu varum, bowing, rotational and wind-swept) were greater in children with dietary calcium deficiency (Tables 2, 3, 4). Laboratory investigations[6,11,14,16,17] revealed high plasma levels of fluoride, alkaline phosphatase, osteocalcin, parathyroid hormone (PTH) and 1,25 $(OH)_2D_3$. Plasma calcitonin concentrations were normal or raised. Plasma calcium, magnesium, phosphorus and 25-OHD_3 concentrations were in the normal range. Raghuramulu *et al*[18] reported elevated serum levels of 25-OHD_3 in subjects suffering from endemic fluorosis and endemic genu valgum. The significance and the factors responsible for the elevated serum 25-OHD_3 are not clear. Biochemical abnormalities were more in calcium deficient children. Twenty four hour urinary excretion of calcium and fluoride was increased in children with calcium deficiency.

TC-99m diphosphonate bone scanning revealed nonspecific appearance of generalised increased tracer uptake throughout the skeleton indicating increased activity of bone tissue with a high metabolic turnover bone disease (fig. 8). Photon densitometric measurements showed increased bone mass (BMD = 0.97 ± 0.45 g/cm^2) in chil-

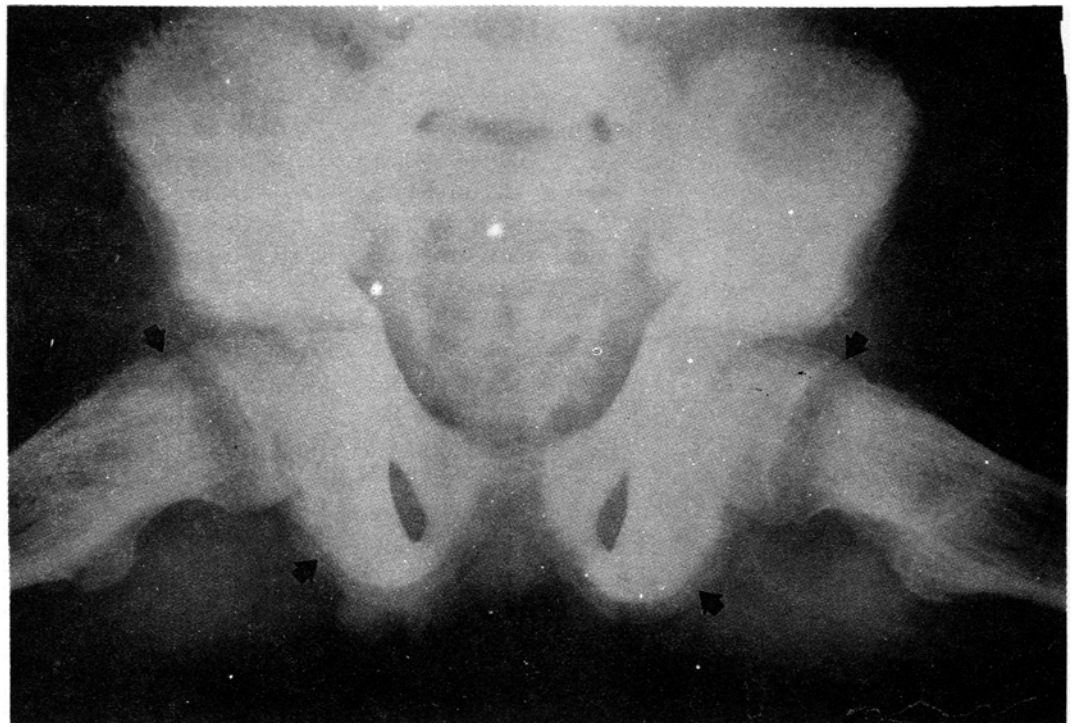

Fig. 4. Radiograph of the pelvis (8 M) showing osteosclerosis with coarse trabeculations, erosions of the femoral neck metaphyses, translucent zone (arrows) of the bone around ileum and the ischio-public rami-the mixture of demineralised (PTH-mediated bone loss) and unmineralised new bone (fluoride induced unmineralised matrix) suggesting fluoride and calcium deficiency interaction with secondary hyperparathyroidism.

dren with adequate calcium intakes as compared to BMD 0.72 ± 0.43 in calcium deficient children.

Histopathological assessment[19, 20] of the undecalcified sections of iliac crest biopsies showed loops and bridges of wide osteoid seams (> 50 μ) covering the calcified trabecular bone surfaces and tunnelling and hook resorption of the bone trabeculae, suggesting high turnover bone disease of rickets associated with secondary hyperparathyroidism caused by high fluoride and low calcium interactions (fig. 9). Repeat biopsy (double tetracycline labelled) taken from the same patient (8 M) 18 months following the supply of normal drinking water (deep bore) with fluoride < 0.5 ppm and instituting correction of calcium deficiency by calcium supplements of 1.5 g/d, revealed mineralisation of the osteoid (clear uptake of labels) and reduction in the trabecular resorption of the bone (fig. 10). These findings indicated histological healing and reversibility of the bone disease caused by high fluoride and dietary calcium deficiency interactions in this child. This observation strongly supports authors' findings previously reported[6,11,13,14]

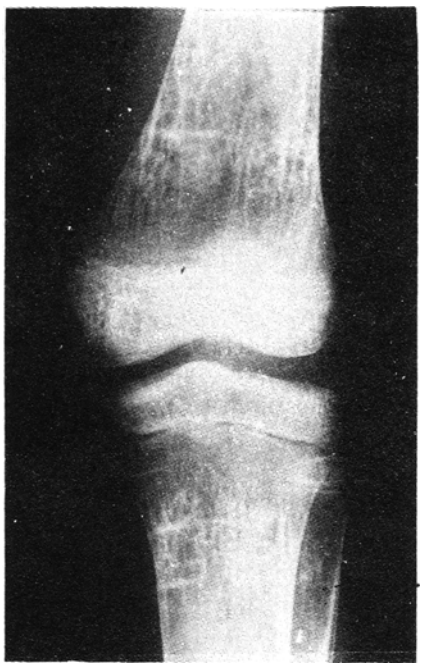

Fig. 5. Radiograph of the knee joint from a patient of endemic skeletal fluorosis (10 M) showing dense bones and epiphyses, axially oriented coarse and cystic trabeculation at metaphyseal and submetaphyseal regions, modelling abnormalities, suggesting hyperparathyroidism secondary to fluoride and calcium interactions.

that providing normal drinking water and improvement of the calcium nutritional status of the community is the most effective strategy in the prevention and control of endemic skeletal fluorosis.

DISCUSSION

All the children studied had skeletal fluorosis as a primary bone disease. The incidence and severity of metabolic bone disease and bony leg deformities was greater and more complex in children with dietary calcium deficiency. The cervical and lumbar spines were more severely affected and

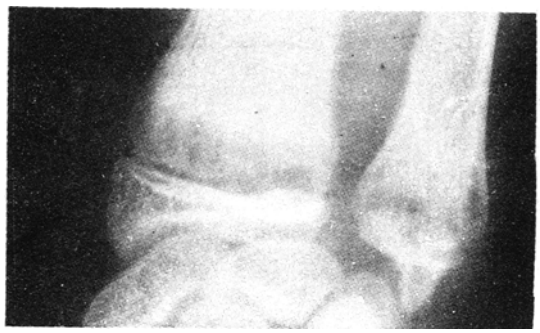

Fig. 6. Radiograph of the wrist from the child of skeletal fluorosis (13 F) showing osteosclerosis, metaphyseal bands of neo-osseousporosis and neo-osseousmalacia in the newly formed bone suggesting early rickets with secondary hyperparathyroidism.

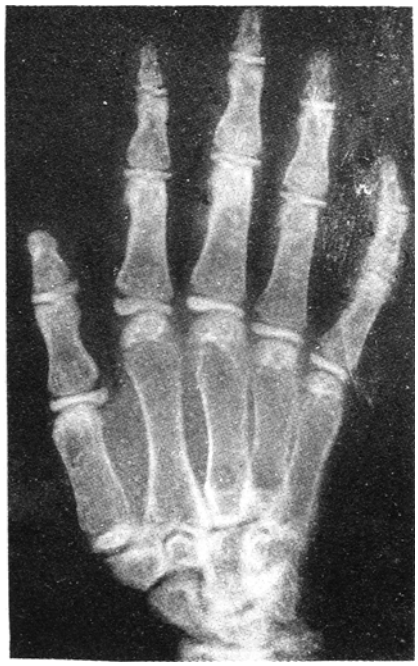

Fig. 7. Radiograph of the hand showing osteosclerosis, dense epiphyses, coarse cystic trabeculations, thin cortices and resorption of cancellous bone with modelling defects in the metacarpal and phalangeal bones in a child of skeletal fluorosis (12 M) with secondary hyperparathyroidism.

caused clinical invalidness. Skeletal transformation into metabolic bone disease (rickets, osteoporosis, PTH bone disease) occurred in 90% of the children with calicum deficiency as compared to 25 percent in children with adequate calcium intake and with comparable intake of water fluoride.

Biochemical abnormalities, as reported by us previously, are significantly greater in children with dietary calcium deficiency ($p < 0.05$). The state of metabolic skeletal transformation is determined by whether the excessive fluoride in drinking water is ingested in the presence of adequate or inadequate calcium nutrition. Thus endemic skeletal fluorosis presents in two major forms (1) as generalised osteosclerosis with minimal biochemical changes usually observed in children with adequate calcium nutrition. (2) skeletal fluorosis associated with metabolic bone disease and deformities with significant biochemical abnormalities, usually occurring in children with inadequate calcium nutrition.

The toxic effects of fluoride are more severe in calcium deficient children because the ingested calcium is not adequate to counter the effects of fluoride and suppress the PTH mediated bone loss which continues unopposed. The syndrome of metabolic bone disease and deformities, in children exposed to high intake of fluoride possibly evolves as a result of the biological impact of high fluoride, low calcium, raised PTH and 1,25 $(OH)_2D_3$ separately and through their interactions on the bone chemistry, structure and bone mineral metabolism. The possible pathophysiological mechanisms involved are summarised in Table 5.

In calcium deficient children the toxic effects of fluoride manifest even at marginally high (> 2.5 mg/day) intake of fluoride. Also the metabolic and endocrine effects of calcium deficiency on bone are further exaggerated in children exposed to fluoride, affecting skeletal function, growth and development.

Fluoride toxicity afflicts children more severely and over a shorter period of exposure (about 6 months) as compared to

TABLE 1. Classification of Severity of Endemic Skeletal Fluorosis

		Clinical
Mild : Generalised bone and joint pains		
Moderate :	+	Stiffness, rigidity and restricted movements at the spine and joints.
Severe :	+	Flexion deformities at the spine, hips and the knees, genu valgum, genu varum, bowing and rotational deformities of legs, neurological complications, crippling and bed-ridden state.
		Radiological
Mild : Osteosclerosis only		
Moderate :	+	Periosteal bone formation, calcifications of interosseous membrane, ligaments, muscular attachments, capsules and tendons.
Severe :	+	Associated metabolic bone disease (rickets neo-osseousmalacia, osteoporosis, neo-osseous-porosis, secondary hyperparathyroidism) exostoses, osteophytosis.

+ = Features added with increasing severity of fluorosis

TABLE 2. Progressive Evolution of Clinical Features in Patients of Endemic Skeletal Fluorosis in Relation to their Calcium Nutrition (Total Cases 45, 725 : 1963-1997)

Calcium intake > 800 mg/day (n = 21,465)		Calcium intake < 300 mg/day (n = 24,260)	
1.0	Asymptomatic : radiological skeletal flourosis only (75%)	2.0	Asymptomatic : radiological skeletal fluorosis only (10%)
1.1	Symptomatic : progressive evolution of symptoms (25%)	2.1	Symptomatic : progressive evolution of symptoms (90%)
1.2	Vague pains, aches, arthralgia	2.2	Vague pains, aches, arthralgia
1.3	+ Backpain, pain in cervical spine, stiffness, rigidity, constipation	2.3	+ Backpain (lumbar and cervical spine)
1.4	+ Limitation of movements at the joints, inability to close fists.	2.4	+ Limitation of movements at the spine and joints
1.5	+ Difficulty in walking, generalised forward flexion, ankylosis at spine, hips, knees and elbows	2.5	+ Stiffness, fixity of spine and chest, inability to close fists.
1.6	+ Inability to walk, extreme fixity of chest and spine	2.6	+ Generalised flexion with ankylosis at spine, hips and knees
1.7	+ Crippling, rarely neurological complications	2.7	+ Coxa vara, genu valgum, genu varum, bowing, rotational and wind-swept deformities at knees and legs (high fluoride and calcium deficiency interaction syndromes)
		2.8	+ Inability to walk and crippling

Clinical syndrome of skeletal fluorosis and associated metabolic bone disease and deformities is more severe and complex in calcium deficient children

+ = Features added with increasing severity of fluorosis

adults. This is because the rapidly growing bones of children are metabolically active and more vascular and thus absorb and accumulate fluoride faster and in greater amounts than older bones, particularly at the sites of bone growth and physiological calcifications. Also, more fluoride is incorporated by bones with a high metabolic turnover. Age of the child at the time of fluoride ingestion, rate of skeletal growth and accumulation of bone mass, duration of exposure to fluoride and the total intake of fluoride per day are other factors which influence the status of bone disease and de-

TABLE 3. Radiological Features in Patients of Endemic Skeletal Fluorosis in Relation to Their Calcium Nutrition (Total Cases, 25, 695 : 1963-1997)

	Calcium > 800 mg/day (n = 12,250)		Calcium < 300 mg/day (n = 13,175)
1.0	Generalised osteosclerosis (spine, pelvis, thorax)	2.0	Generalised osteosclerosis with coarse axially oriented trabeculations particularly in the metaphyses and sub-metaphyseal regions of long bones, neo-osseousporosis, neo-osseousmalacia
1.1	Irregular periosteal bone formation (Around elbows)		
1.2	Dense and thick cortex with reduced and an uneven marrow cavity	2.1	Dense epiphyseal lines, epiphyses, metaphyses and modelling abnormalities in the metacarpal, tarsal and the phalangeal bones.
1.3	Evidence of secondary hyperparathyroid bone disease	2.2	Rickets, ricketic metaphyses, secondary hyperparathyroidism, sub-metaphyseal bands of osteoporosis.
1.4	Calcifications of interosseous membrane, ligaments, muscular attachmens, capsules and tendons (rare < 5%)	2.3	Thin cortices, microcystic expansion of trabecular bones.
1.5	Irregular osteophytosis and exostoses (rare < 5%)	2.4	Calcifications of interosseous membrane ligaments, muscular attachments, capsules and tendons (rare < 5%)

Calcifications of interosseous membrane are rare below the age of 14 years.

Syndromes of skeletal fluorosis and associated metabolic bone disease and deformities were severe and complex in children with dietary calcium deficiency.

TABLE 4. Severity of Skeletal Fluorosis in Relation to Calcium Nutrition of the Children Studied (Total Children = 45,725 M = 24,260 F = 21,465)

Calcium intake mg/day	No. of children	Age range	Mean water F -(PPM)	MeanF-intake mg/d	Severity of skeletal flurosis		
					Mild	Moderate	Severe
Adequate > 800	23,470	4-16	5.23 ± 1.03	9.6 ± 2.2	89	9.0	2.0
Inadequate < 300	22,255	4-16	5.29 ± 1.06	9.7 ± 2.8	10	55	35

*All the children had normal vitamin-D nutritional status due to adequate skin exposure to sunlight

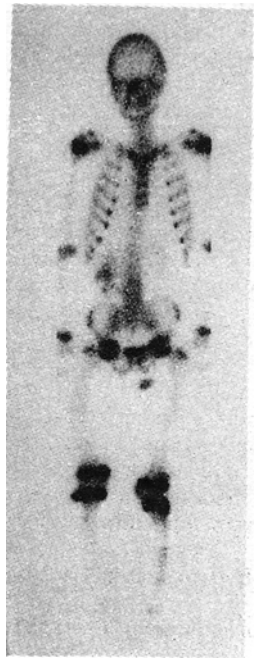

Fig. 8. TC-99 m bone scan revealing nonspecific appearance of generalised increased tracer uptake throughout the skeleton indicating increased activity of bone tissue with a high metabolic turnover bone disease.

formities

In view of our extensive experience we suggest that children with calcium deficiency rickets reported in the literature need to be re-investigated for their possible interactions with fluoride. We believe that calcium deficiency per se does not cause rickets. This aspect has not been analysed in any of the reports published on calcium deficiency rickets. A greater index of clinical acumen is, therefore, necessary to differentiate calcium disorders in childhood from fluoride and calcium interaction syndromes of bone disease and deformities, particularly when the child presents with skeletal symptoms of greater variety and

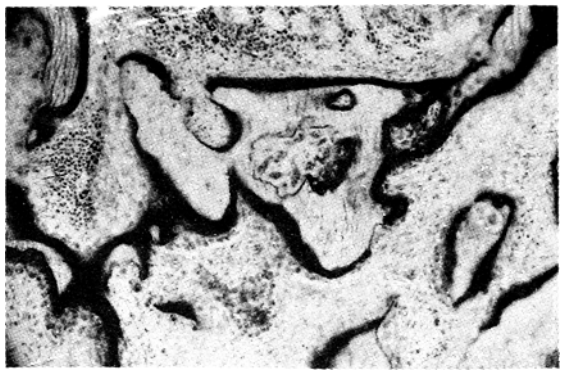

Fig. 9. Histopathological picture of the undecalcified section of iliac crest biopsy showing loops and bridges of wide osteoid seams (> 50 μ) and tunnelling resorption of the bone trabeculae suggesting rickets with secondary hyperparathyroidism in a child (8 M) with endemic skeletal fluorosis (x 100).

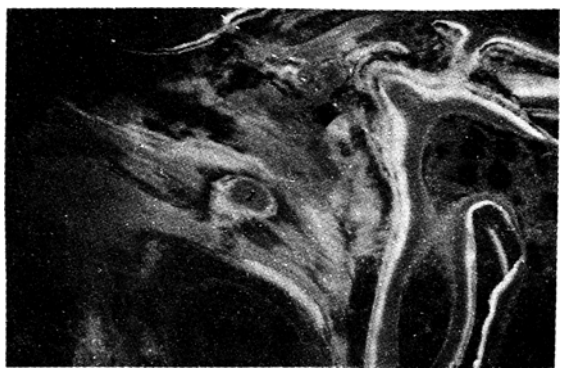

Fig. 10. Histomorphometric picture of double tetracycline labelled iliac-crest biopsy taken from the same child (8 M) 18 months following the supply of normal drinking water (F - < 0.5 ppm) and calcium supplements of 1.5 g/d showing marked reduction in the osteoid and trabecular resorption with clear uptake of labels indicating reversibility and healing of rickets caused by high fluoride and low calcium interactions.

TABLE 5. Metabolic and Endocrine Events in the Evolution of High Fluoride and Low Calcium Interaction Syndromes of Metabolic Bone Disease and Deformities Involving the Parathyroid Hormone and 1,25 $(OH)_2D_3$ Endocrine System. (Modified from Teotia and Teotia JAPI, 32, 347, 1984)

Cells		Mineral	Matrix
Stimulation of osteoblasts	Osteosclerosis	Hydroxyapatite	Impaired collagen synthesis and Metabolism
↓	↑	↓	↓
Increased organic matrix of bone (Osteoid)	Adequate	Fluoroapatite	Abnormal, immature, Poorly calcifiable new Matrix
↓ Fluoride induced inhibition of mineralisation	↑ Calcium nutrition* ↓	↓ Bone crystals more stable, less reactive, resistant to parathomone	↓
Impaired Mineralisation	Inadequate	↓	Amorphous, woven hypomineralised bone
↓	↓		↓
Rickets	Low plasma calcium	Low plasma ionised calcium	Rickets
↓	↓	↓	↓
Secondary hyperpara-thyroidism (PTH Bone Disease)	Secondary hyperpara-thyroidism [Increased 1,25 $(OH)_2D_3$]	Secondary hyperpara-thyroidism [Increased 1, 25 $(OH)_2D_3$]	Secondary hyperapara-thyroidism (PTH Bone Disease, Osteoporosis)

*Adequate calcium nutrition counteracts and suppresses the toxic effects of fluoride on bones, while the inadequate calcium nutrition exaggerates and makes the toxic effects of fluoride more severe and complex.

unusual, raising a diagnostic problem. We believe that every child living in areas endemic for fluorosis and presenting with bone disease is a case of skeletal fluorosis unless proved otherwise.

Providing of deep bore water (fluoride < 0.5 ppm) and the concurrent programme aimed at correction of the nutritional imbalance especially of the calcium intake (1-2 g/day) of the affected and the community at risk gives a 100% protection against the toxic effects of fluoride on bones.[21]

The authors believe that this most comprehensive and single largest epidemiological study on endemic skeletal fluorosis in the world literature - is based on our personal research and experience of over more than thirty years (1963-1997) studying the effects of endemic fluoride in drinking water on human skeleton in relation to the community calcium nutrition status.

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