Fluoride and Osteoporosis (42921)

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There is extensive literature concerning the action of fluoride on the skeleton. Numerous studies indicate that fluoride treatment appropriately applied could augment trabecular bone mass and inhibit fractures in osteoporosis (1, 2). It has been proclaimed as the "single most effective agent" for osteoporosis (3). However, several problems have kept this drug from approval by the FDA; they include frequent gastrointestinal and rheumatic complications, nonresponsiveness in some patients, and the concern that it may cause the formation of a mechanically defective bone (1).

There is emerging evidence which indicates that these problems could be overcome. After a brief discussion of historical background, this presentation reviews the role of fluoride in osteoporosis from the perspective of pharmacokinetics, physicochemistry, physiology, biochemistry; effects on histomorphometry, mass, and mechanical properties of bone; and finally of clinical response and side effects.

Historical

That fluoride could augment skeletal mass has been appreciated for at least 100 years. Exaggerated bone growth has long been known to occur in areas of endemic fluorosis. More recently, several epidemiologic studies disclosed that fluoridation of domestic drinking water may protect against the development of osteoporosis. Leone *et al.* (4) found a reduced occurrence of vertebral osteoporosis in Bartlett County, Texas, with a fluoride content in drinking water of 8 mg/liter compared with that in Farmington, Massachusetts with a fluoride content of the drinking water of 0.09 mg/liter. Bernstein *et al.* (5) found low prevalence of vertebral fractures among women in regions of North Dakota where drinking water was fluoridated than in regions which were not fluoridated. Similarly, Simonen and Laitinen (6) reported a reduced prevalence of femoral neck fractures in Finnish towns of Kuopio with a fluoride content in the drinking water of 1 mg/liter than in Jyvaskyla with a fluoride content in the drinking water of 0.1 mg/liter. However, two other reports found no beneficial effect of fluoride in protecting against the development of osteoporosis. The National Health Interview surveys in 1973 found no effect of fluoride content in the drinking water of 0.7 mg/liter on the development of hip fracture (7). Sowers *et al.* (8) reported no difference in the fracture rate in the region in northwest Iowa with a fluoride content of 4 mg/liter vs that containing 1 mg/liter.

These discrepant findings are not unexpected. The usual fluoride content of 1 mg/liter of fluoridated water is considerably below that normally required for skeletal growth (approximately 20 mg/day). Thus, fluoridated water at this customary level must be consumed for many years before a protective effect against the development of osteoporosis would occur.

Pharmacokinetics

Intestinal Absorption of Fluoride. Fluoride absorption from the intestinal tract occurs passively; there is no evidence for active transport (9). Absorption of fluoride occurs largely in its undissociated form (hydrofluoric acid) (10). In the stomach, the undissociated fluoride predominates, since its luminal pH is often less than the pK_a of hydrofluoric acid of 3.4. Thus, the stomach is the principal site of fluoride absorption. Fluoride is also absorbed in its anionic form in the intestinal tract distal to the stomach, but to a lesser degree as the undissociated hydrofluoric acid. Fluoride absorption is therefore impaired in patients with defective acid secretion and in those receiving antacids or H_2 blockers. It is also impeded following ingestion of milk (11) or calcium (12) due to formation of calcium fluoride of low aqueous solubility. No homeostatic regulation for fluoride absorption has been recognized (13).

Renal Handling. Fluoride is freely filtered in the kidneys. Some of the filtered fluoride is reclaimed by tubular-back diffusion. Thus, there is a close correspondence of filtered water and urinary fluoride (14, 15). Fluoride clearance normally averages 65 ml/min, with a higher value approximating the glomerular filtration rate under a high fluid intake and falling below this value during inadequate fluid intake (15). The only route of fluoride disposal is the renal excretion. When fluoride in a rapid release form is given by mouth alone, it is quickly absorbed, reaching peak concentration in blood within 2–3 hr. The fraction of fluoride that is not deposited in bone appears in the urine rapidly, with a lag time between blood and urine levels of only 1–2 hr

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(16). Fluoride is present largely in its ionic form in the circulation (17).

Fluoride Uptake by Bone. Within the first 3 months of fluoride therapy, approximately 50% of absorbed fluoride is deposited in bone, the remainder appearing in urine (9). After bone becomes saturated, absorbed fluoride largely appears in urine. Data on skeletal fluoride content following fluoride therapy are sparse because of the requirement for bone biopsy. Although a preliminary report indicated that skeletal fluoride content may be assessed by nuclear magnetic resonance (18), further refinement and quantitation are required. Nevertheless, available data suggest that serum fluoride level provides a reflection of skeletal fluoride content (19). Moreover, the skeletal fluoride content correlates with the expected histomorphometric changes of fluoride in bone (19).

Therapeutic Window. For reasons described above, it has been customary to utilize fluoride concentration in serum in order to monitor sodium fluoride dose in the management of osteoporosis. Recognizing this concept, Taves (20) first established the therapeutic window for fluoride in serum at 5–10 μm (95–195 ng/ml). According to this scheme (Fig. 1), serum fluoride level should be at least 95 ng/ml before a beneficial effect on the skeleton would be obtained and that it should be kept below 190 ng/ml if toxic effects (rheumatic complications) are to be avoided. This concept is supported by the finding that dental or enamel fluorosis has been reported at serum fluoride concentration exceeding 190 ng/ml (21). In our own experience, patients presenting with rheumatic complications during long-term fluoride therapy had a mean trough fluoride concentration in serum of 278 ng/ml. The mean serum fluoride concentration was 127 ng/ml in patients free of rheumatic complications. Harrison *et al.* (22) reported that skeletal calcium content increased when serum fluoride level was kept between 72 and 165 ng/ml, whereas it decreased when serum fluoride level was kept below 91 ng/ml.

Bioavailability of Different Sodium Fluoride Preparations. Following administration of a plain sodium fluoride preparation, serum fluoride level reaches a sharp peak rapidly (Fig. 2) (23), reflecting optimum absorbability of undissociated sodium fluoride. Thereafter, serum fluoride rapidly declines to the basal level within 12 hr. Thus, a long-term, twice daily administration of sodium fluoride in a plain form produces two sharp peaks and valleys in serum daily, with peaks exceeding toxic threshold and valleys falling below therapeutic threshold (24).

In contrast, following oral administration of sodium fluoride in a slow release form (Slow-Fluoride, Mission), serum fluoride concentration rises more slowly, reaching a peak at about 4–5 hr, reflecting absorption of fluoride anion distal to the stomach (Fig. 2) (23). Therefore, it declines slowly, maintaining a value above the basal level even at 12 hr. Thus, twice daily administration of Slow-Fluoride results in the maintenance of serum fluoride level within the therapeutic window, with only a modest circadian fluctuation (23). This property may be critical in assuring safety of usage and in obviating formation of mechanically defective bone (to be discussed).

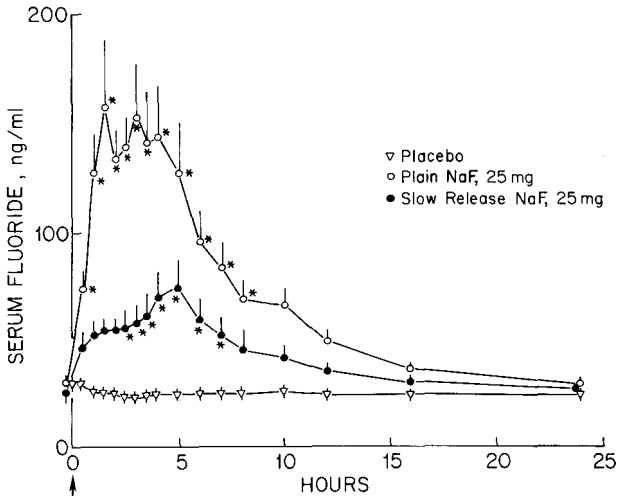

Figure 2. Fluoride bioavailability in eight normal subjects who had not been on sodium fluoride treatment. The arrow indicates the time when a single dose of placebo, plain sodium fluoride (25 mg), or slow release sodium fluoride (25 mg) was administered orally. The significant difference from the placebo phase is shown by * for $P < 0.05$. Mean and SEM are shown (adapted from Pak *et al.* (23)).

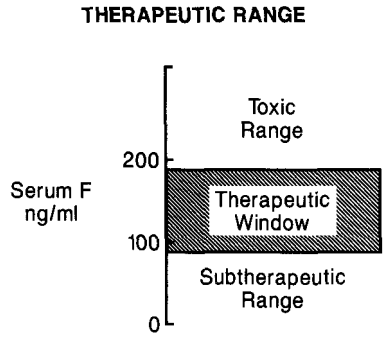

Figure 1. Therapeutic window for serum fluoride.

Physicochemistry

The physicochemical effect of fluoride on the skeleton is well known. The reaction of fluoride with hydroxyapatite of the bone mineral results in the formation of fluoroapatite from the substitution of hydroxyl ions by fluoride ions (25). Fluoroapatite is more crystalline (25) and has a larger crystalline size and lower solubility than hydroxyapatite (26). Bone powder from fluoride-treated animals has a preponderance of higher density fractions than from untreated animals (27). Partly owing to these physicochemical properties, the fluoride-treated bone is less subject to dissolution (28).

Physiologic Actions of Fluoride

During long-term treatment with fluoride, no change in intestinal calcium absorption has been observed (29). However, a decline in urinary calcium excretion has been noted (29), a finding attributed to the skeletal retention of calcium produced by fluoride.

No significant change in serum calcium or phosphorus has been reported (30). Serum immunoreactive parathyroid hormone is typically normal when fluoride is given with an adequate amount of calcium or vitamin D. A rise in urinary nondialyzable hydroxyproline (30) and in serum osteocalcin concentration (23) may occur, indicative of osteoblastic stimulation. At high doses of fluoride, serum alkaline phosphatase may increase (3).

Biochemistry

Fluoride is capable of stimulating osteoblasts (31, 32). In isolated osteoblast-like cells in culture, fluoride has been shown to cause cellular proliferation, increase alkaline phosphatase activity, and stimulate collagen synthesis and calcium deposition (31).

Molecular mechanisms for fluoride action are less well elucidated. Fluoride acts on a GTP-binding regulatory protein that is distinct from cyclase itself and acts as an intermediary regulator between receptor and cyclase (33). Thus, increased adenyl cyclase activity has been shown in isolated bone cells (34) following fluoride exposure, and the tissue content of cyclic AMP in bone has been shown to be raised after fluoride therapy (35). In addition, fluoride has been shown to inhibit magnesium-calcium-ATPase in cultured osteoblast-like cells (36). It is intriguing to speculate that fluoride exerts its action by enhancing cytosolic ionic calcium concentration achieved by either of above two means. Recently, another scheme for fluoride action on osteoblasts was suggested. Fluoride could also increase cytosolic calcium by influencing phosphatidyl inositol pathway (37). Fluoride was shown to inhibit phosphotyrosyl phosphatase of osteoblasts (38). The resulting rise in intracellular levels of phosphotyrosine could then lead to stimulated osteoblast proliferation.

There is some evidence that fluoride at high concentrations may exert a toxic effect on osteoblast function. Following a long-term exposure to fluoride, especially at high doses, osteoblasts assume a flat, inactive appearance (1). Histomorphometric analysis of bone has disclosed that both bone formation rate and resorption rate are reduced at each bone multicellular unit, indicative of toxic effect on bone cells (39). Following long-term exposure to fluoride, the amount of osteoid surfaces covered by osteoblasts are decreased, suggestive of reduced osteoblastic activity (1). Moreover, fluoride therapy at a high dosage has been shown to be associated with the synthesis of collagen with defective cross-linking (40) and with an overproduction of dermatan sulfate, an inhibitor of calcification (41–43). These effects may cause impaired mineralization of bone. These findings emphasize the need to provide fluoride in a form (e.g., slow release) which allows maintenance of serum fluoride at a therapeutic but subtoxic level in serum.

Bone Histomorphometry following Fluoride Therapy

The principal action of fluoride is the stimulation of appositional growth on existing surfaces (44, 45). Thus, it is capable of increasing the thickness of existing trabeculae (46). There is recent evidence that fluoride may cause focal osteoclastic resorption. Thus, fluoride treatment could allow remodeling of bone and increase the number of bone multicellular units.

The effect of fluoride on histomorphometric picture of bone depends on the fluoride dosage and on whether it is given alone or with calcium. When fluoride is given, especially at a high dosage without calcium, osteomalacia may develop (47, 48). The newly formed matrix may be abnormal and may not undergo adequate mineralization. Thus, a typical histomorphometric picture is represented by a pronounced increase in osteoid (nonmineralized matrix) and reduced calcification front. The formation of abnormal, fibrous, or mosaic bone may occur.

When fluoride is given with an adequate calcium intake, the newly formed matrix may become adequately mineralized. Typical changes include an increase in trabecular bone volume without a substantial change in osteoclastic resorption surface or calcification front (49–51). A modest increase in total osteoid surface and osteoid seam has been demonstrated; however, these changes do not approach those encountered in osteomalacia. The impairment in mineralization may become less severe with continued therapy (52). However, approximately 15% of patients may show mild osteomalacia and 25% of patients may not show any histologic response (49). In our study of slow release sodium fluoride with calcium citrate, histomorphometric analysis of bone has disclosed an increased formation of normally appearing, lamellar bone, which was adequately mineralized (53).

Effect of Fluoride Treatment on Bone Mass

There are six studies which examined the effect of long-term fluoride treatment on spinal bone mass (Table I) (22, 54–57). The dose of sodium fluoride varied from 30 to 80 mg/day, and the duration of treatment ranged from 1.2 to 3 years/patient. One study measured total skeletal calcium content (CaBI) by neutron activation (22). Three studies assessed bone mass by dual photon absorptiometry (DPA) and two studies by quantitative computed tomography (CT). All six studies reported an increase in spinal bone mass, ranging from 2.9 to 23.5% per patient/year. A rise in bone mass was greater in two studies using CT, probably reflective of the greater sensitivity to fluoride action of the trabecular bone, the density of which this technique measures.

In contrast, fluoride treatment had a variable effect on the bone mass at other sites (Table II) (30, 54, 57–

60). The bone mass of the metaphysis or diaphysis of long bones increased slightly during fluoride treatment, except in one study (60) in which it decreased probably due to a low dose of sodium fluoride utilized (20 mg/day). One report found a rise in bone mass of the femoral neck while another disclosed a reduction.

Three of the studies which examined the effect of fluoride treatment on spinal bone mass included a control group (Table III) (22, 54, 55). Whereas the treated group showed a rise in bone mass, one control study showed a less prominent rise and two disclosed a reduction in spinal bone mass. Three other studies examined bone density at other sites in subjects who were not receiving sodium fluoride (30, 59, 60). All three showed a reduction in bone mass of the distal tibia, distal radius, or finger without fluoride treatment.

Thus, it is apparent that fluoride treatment augments spinal bone mass without causing a loss of bone at other sites. The increment in spinal bone mass found in our trial with slow release sodium fluoride (Slow-Fluoride) was comparable to that reported by two other studies using dual photon absorptiometry (Fig. 3).

Mechanical Properties

It has been alleged that bone becomes mechanically defective after long-term fluoride treatment, due to the formation of fluoroapatite or to a defect in mineralization. There are scanty studies concerned with the examination of mechanical properties of human bone following fluoride treatment. Available data are largely confined to animal studies and endemic fluorosis.

Mechanical properties of bone have been examined from the resistance to compressive forces and that to torsional strain. The fracture load per area of human vertebra, reflective of resistance against compressive force, was shown to be substantially increased in fluorotic bone compared with control bone (61). In immobilized rat vertebra, the breaking strength indicative

Table I. Effect of Fluoride Treatment on Spinal Bone Mass

Authors	No. of patients	Dose NaF (mg/day)	Duration (year)	Method	Change (%)	
					Total	Per year
Harrison *et al.*, 1981 (22)	8	50	3	CaBI	12.7	4.2
Raymakers *et al.*, 1987 (53)	53	50–75	1.2	DPA	3.6	2.9
Hansson and Roos, 1987 (54)	24	30	3	DPA	17.0	5.7
Duursma *et al.*, 1987 (55)	13	40–80	2	CT	47.0	23.5
Juhn *et al.*, 1988 (56)	90	1 mg/kg	?	CT	?	9.0
Pak *et al.*, 1989 (80)	21	50	2.9	DPA	11.8	4.1
Combined	209				13.1	7.3

Table II. Effect of Fluoride on Bone Mass at Other Sites

Authors	No. of patients	Dose NaF (mg/day)	Duration (year)	Site	Change (%)	
					Total	Per year
Farley *et al.*, 1987 (3)	30	66–95	2	Distal radius	2.0	1.0
Farley *et al.*, 1987 (32)	30	66–95	2	Radial shaft	2.0	1.0
Dambacher *et al.*, 1986 (58)	15	80	2	Distal tibia	1.0	0.5
Christiansen *et al.*, 1980 (59)	25	20	2	Distal radius	−3.6	−1.2
Juhn *et al.*, 1988 (56)	90	1 mg/kg	?	Femoral neck	?	4.5
Manzke *et al.*, 1977 (30)	20	20–40	2.1	Finger	−0.14	−0.07
Raymakers *et al.*, 1987 (53)	53	50–75	1.2	Femoral neck	−0.7	−0.5

Table III. Changes in Bone Mass in the Control Group

Authors	No. of patients	Duration (year)	Site	Method	Change (%)	
					Total	Per Year
Harrison *et al.*, 1981 (22)	6	3	Spine	CaBI	2.1	0.7
Raymakers *et al.*, 1987 (53)	18	1.1	Spine	DPA	−1.7	−1.5
Hansson and Roos, 1987 (54)	19	3	Spine	DPA	−0.03	−0.01
Dambacher *et al.*, 1986 (58)	14	2	Distal tibia	CT	−6.6	−3.3
Christiansen *et al.*, 1980 (59)	103	2	Distal radius	SPA	−3.3	−1.7
Manzke *et al.*, 1977 (30)	20	2.1	Finger	X-ray	−5.2	−2.5
Combined	180				−3.09	−1.36

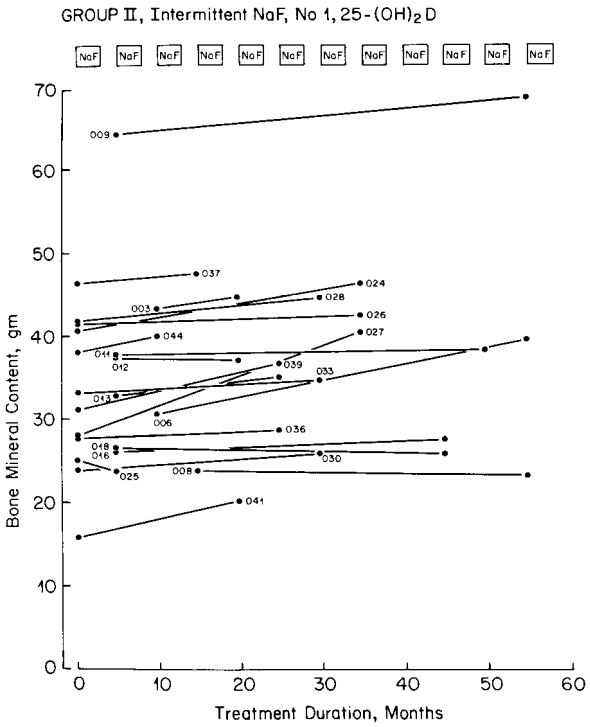

Figure 3. Effect of long-term sodium fluoride therapy on vertebral bone mineral content in patients receiving intermittent slow release sodium fluoride (25 mg three times a day, for 3 months of every 5 months) with calcium citrate. Continuous lines indicate the first and the last measurement in the same patient. The numbers adjacent to lines indicate patient study codes.

of resistance against compressive force was substantially increased when rats were treated with fluoride, particularly with calcium (62). These results indicated that fluoride produces increased resistance to compressive forces, possibly by augmenting the total mass of bone.

However, the resistance against torsional strain was reduced following fluoride treatment. Thus, the femur of fluoride-treated animals showed low values for stress at fracture, stiffness, and torque, and a higher value for flexibility (63). These changes were much less marked when animals were fed fluoride with calcium (64).

Despite limited data, the following conclusions may be drawn. Fluoride treatment increases the resistance against compressive forces on the vertebra. Thus, fluoride provides protection against vertebral fracture. However, when fluoride is given alone especially at high doses, the poorly mineralized bone may lead the long bones to increased risk of fracture. This problem may be alleviated by provision of calcium with fluoride, allowing for adequate mineralization of newly formed bone. Avoidance of toxic levels of fluoride with a slow release sodium fluoride preparation may further assure adequacy of bone mineralization and minimize risk for fractures of long bones. In our study with Slow-Flouride and calcium citrate, hip fractures were uncommonly encountered.

Effect of Fluoride Treatment on Fracture Rates

Six long-term trials with sodium fluoride, involving 164 patients with osteoporosis, have been reported (Table IV) (49, 58, 65–67). The dose of sodium fluoride ranged from 40 to 110 mg/day, and the duration of treatment ranged from 1.5 to 4.1 years/patient. In these studies, the fracture rate of the vertebra during treatment ranged from 50 to 304 fractures per 1000 patient years, yielding an average fracture rate during fluoride treatment (corrected for number of patients) in combined trials of 207 fractures per 1000 patient years.

None of the studies described above included a randomly allocated placebo-controlled group. However, there are four studies in which a control group or a group taking no medication had been included (Table V) (59, 65, 67). Among 108 patients followed from 2 to 4.5 years/patient, the vertebral fracture rate ranged from 250 to 834 per 1000 patient years for an adjusted mean rate of 554 per 1000 patient years.

The above higher figure in the control group (554 vs 207) supported the contention that fluoride therapy reduces vertebral fracture rate. The effect of slow release sodium fluoride was equivalent to that of other preparations (Fig. 4).

Side Effects of Fluoride Therapy

Complications of plain or coated sodium fluoride therapy were reviewed from nine published reports involving 413 patients with osteoporosis (Table VI) (19, 22, 55, 61, 65, 66, 68–70). Gastrointestinal complications usually comprised minor adverse symptoms such as cramping, nausea, or diarrhea. Symptoms were sometimes more severe, involving gastrointestinal bleeding. These gastrointestinal complications ranged from 6 to 50% of patients among various series, with a mean figure of 23.5% (corrected for number of patients). Rheumatic complications included joint pain, plantar fascitis, and synovitis. They ranged from 15 to 37% for a mean of 29.0%.

In four studies where a slow release form of sodium fluoride was utilized, adverse reactions were less common, with gastrointestinal complications of 6.4% and rheumatic side effects of 19.1% (Table VII) (56, 59, 71). These findings could be attributed to the limited formation of corrosive hydrofluoric acid in the gastric lumen due to the delayed release of fluoride, and to the possible avoidance of sharp peaks in blood exceeding toxic threshold due to a less efficient absorbability of fluoride in its anionic form.

It is now believed that the articular pain occuring during fluoride therapy is the result of microfractures (72, 73). It is generally relieved by temporary withdrawal of fluoride therapy.

It has been suggested that long-term fluoride therapy may exaggerate the risk of hip fractures (74). In a recent study, however, compiled data from five sites

Table IV. Effect of Fluoride Therapy on Vertebral Fracture

Authors	No. of patients	Dose NaF (mg/day)	Duration (year)	Fracture rate (no./1000 patient years)
Farley *et al.*, 1988 (57)	18	66–110	2	50
Riggs *et al.*, 1982 (64)	33	50–60	4.1	304
Lane *et al.*, 1984 (65)	10	60	1.8	143
Power and Gay, 1986 (66)	25	40–60	1.5	230
Meunier *et al.*, 1984 (48)	57	40–75	2.0	220
Pak *et al.*, 1989 (80)	21	50	2.9	160
Combined	164			207

Table V. Vertebral Fracture Rate in the Control Group

Authors	No. of patients	Treatment	Duration	Fracture rate (no./1000 patient years)
Riggs *et al.*, 1982 (64)	45	Placebo/none	2.0	834
Riggs *et al.*, 1982 (64)	27	Calcium	3.7	419
Dambacher *et al.*, 1986 (58)	12	None	3.0	420
Power and Gay, 1986 (66)	24	Calcium	4.5	250
Combined	108			554

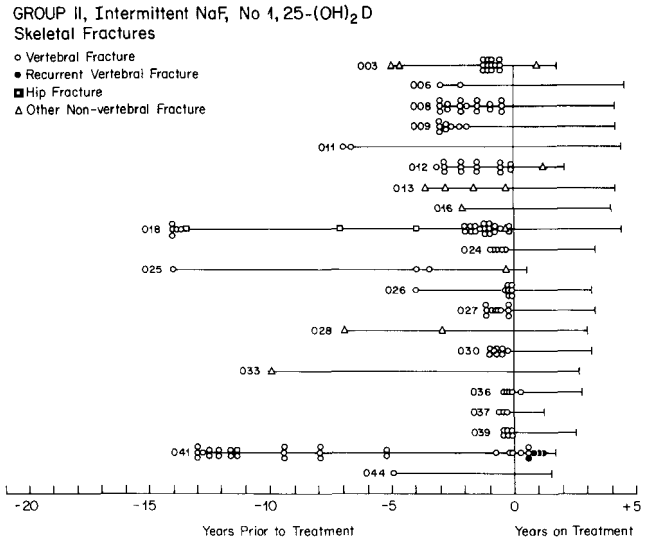

Figure 4. Effect of long-term sodium fluoride therapy on skeletal fractures in patients receiving intermittent slow release sodium fluoride (25 mg twice a day, for 3 months every 5 months) with calcium citrate. Each line represents separate patient. Each symbol indicates separate fracture episode. Closed circles show recurrent fractures on already involved vertebra. Numbers preceding each line represent patient study codes.

did not disclose a higher rate of fracture of the proximal femur than in the untreated population (75). It was noteworthy that patients who sustained femoral neck fracture were often those who took a high dose of sodium fluoride (75). The finding suggested the possibility that an inadequate mineralization of bone from a high fluoride dose may have contributed to femoral neck fracture. It is apparent that this complication could be obviated by avoiding a high dose of sodium fluoride and by taking calcium supplementation to assure adequate mineralization. The rare occurrence of hip fractures with slow release sodium fluoride suggests that avoidance of sharp toxic peaks of fluoride in serum may further be useful.

The skeletal complication of fluoride is more common in renal disease. Because of the impairment in renal excretion of fluoride, high circulating concentrations of fluoride may be achieved in renal disease (76, 77). Osteomalacia and the development of abnormal fibrous or mosaic bone have been described. The dose of fluoride should be carefully monitored in patients with renal disease.

Miscellaneous Effects of Fluoride

In patients receiving long-term steroid treatment, osteoporosis commonly develops from the direct impairment of osteoblastic activity by steroids and the indirect stimulation of osteoclastic resorption from secondary hyperparathyroidism. The latter disturbance may be controlled by treatment with 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D (78). However, the treatment with vitamin D metabolites does not totally avert the development of osteoporosis, because the steroid-induced osteoblastic depression remains. The use of fluoride in this condition would seem obvious, because of the well-known action of fluoride in stimulating osteoblasts. There is some evidence that fluoride may be helpful in averting steroid-induced osteoporosis (79).

Fluoride has been shown to reduce the deposition

Table VI. Adverse Reactions to Sodium Fluoride

Authors	No. of patients	NaF Preparation	Gastrointestinal (%)	Rheumatic (%)
Riggs *et al.*, 1982 (64)	61	Plain	23.0	16.0
Hansson and Roos, 1987 (54)	24	Plain	21.0	?
van Kesteren *et al.*, 1982 (19)	13	Plain	50.0	15.0
Franke *et al.*, 1974 (60)	33	Plain	?	24.0
Kuntz *et al.*, 1984 (67)	19	Plain	32.0	16.0
Lane *et al.*, 1984 (65)	10	Plain	?	20.0
Hasling *et al.*, 1987 (68)	163	Plain	25.0	37.0
Harrison *et al.*, 1981 (22)	16	Plain	6.0	25.0
Briancon and Meunier, 1981 (69)	74	Coated	21.5	32.0
Combined	413		23.5	29.0

Table VII. Adverse Reactions to Sodium Fluoride

Authors	No. Patients	NaF Preparation	Gastrointestinal (%)	Rheumatic (%)
Lie *et al.*, 1982 (70)	13	Slow release	8.0	8.0
Dambacher *et al.*, 1986 (58)	15	Slow release	7.0	47.0
Duursma *et al.*, 1987 (55)	56	Slow release	?	27.0
Pak *et al.*, 1989 (80)	64	Slow release	6.0	7.9
Combined	148		6.4	19.1

of calcium in the kidneys in the animals fed a nephrocalcinogenic diet. It is noteworthy that Berstein *et al.* (5) found reduced prevalence of aortic calcification among subjects living in areas in which the drinking water had been fluoridated. The mechanism for the apparent inhibition of soft tissue calcification by fluoride remains obscure.

Conclusion

There is substantial evidence that fluoride could play a major role in the treatment of established osteoporosis. If properly applied, this treatment could augment vertebral bone mass and inhibit fractures.

However, certain problems of fluoride therapy have limited its wider applicability or acceptance. First, it has a very narrow therapeutic window. Thus, it has been difficult to maintain blood fluoride level above the therapeutic threshold without exceeding the toxic threshold. Second, fluoride treatment has been associated with frequent gastrointestinal and rheumatic complications, approximating 24 and 29%, respectively. Third, fluoride treatment may cause the formation of a mechanically defective bone. Fourth, fluoride may be toxic on osteoblasts at high concentrations. Thus, the beneficial effect of fluoride may be self-limiting. Finally, 25–30% of patients may not respond to fluoride.

It is our conviction that these limitations of fluoride therapy may be largely overcome by the intermittent application of a slow release preparation of sodium fluoride combined with an optimally bioavailable calcium supplement. Using Slow-Fluoride with calcium citrate, it has been possible to maintain serum fluoride concentrations within the therapeutic window for extended periods. In so doing, rheumatic complications have been minimized. Moreover, gastrointestinal complications have been few due to the limited release of fluoride in the stomach to form the corrosive hydrofluoric acid. By providing calcium citrate with slow release sodium fluoride, vertebral bone mass has increased without a reduction in the radial or femoral bone mass. The new bone formed as lamellar in appearance, adequately mineralized, and apparently intact mechanically. Vertebral fracture rate substantially declined during treatment. Finally, the majority of patients responded favorably to treatment with a rise in bone mass and a reduction in fracture rate. Failures were few and accountable largely to inadequate fluoride level achieved in serum due to noncompliance or subnormal dosage.

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