MEDICAL MANAGEMENT OF ESTABLISHED OSTEOPOROSIS: ATTEMPTS AT AUGMENTATION OF BONE MASS

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Osteoporosis is a common disease, constituting a major medical problem(1). Substantial progress has been made in the pathogenesis and management of this condition in recent years. Particularly noteworthy have been advances made in the prevention of bone loss leading to osteoporosis in the postmenopausal state. There is convincing evidence that estrogen therapy is effective in the prevention of the loss of both cortical and trabecular bone during estrogen-lack(2,3). There is preliminary study suggesting that calcitonin may be equally effective, especially in patients with a high turnover state of bone(4). Despite ongoing controversy, calcium supplementation and a regular physical exercise program may be useful(2,5,6).

However, results of treatment of patients with established osteoporosis, after bone loss and fractures have occurred, have been disappointing. In such patients, treatments directed simply at the prevention of further bone loss are often not good enough, since the prevailing reduced bone mass would expose them to continued susceptibility for fractures. An effective management of established osteoporosis should therefore be directed at the augmentation of bone mass(7). Unfortunately, there is as yet no drug approved by the FDA subserving this purpose.

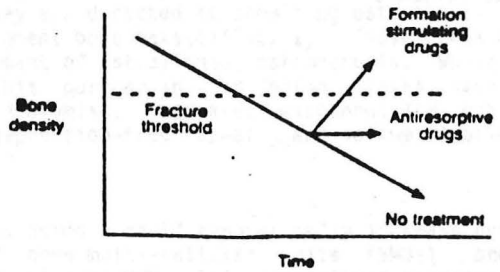
Recent studies indicate that several investigational approaches may provide a safe and effective augmentation of bone mass. Some of these approaches are currently undergoing a multi-clinic trial. One such trial has been initiated by the Dallas Area Osteoporosis Study and Management Group. Thus, it is realistic to expect that approved drugs would be available to the practicing physician for the treatment of established osteoporosis in a foreseeable future. This anticipation provides the justification for my commitment of this Grand Round, the fourth in the area of osteoporosis, to the discussion of current investigative attempts at the augmentation of bone mass. A major consideration shall be given to the role of fluoride, an area of intense research in my laboratory and the approach which is currently undergoing confirmatory trial by the Dallas Area Osteoporosis Study and Management Group. This discussion will consider mainly primary osteoporosis, particularly that which occurs in the postmenopausal state.

TWO BROAD TYPES OF DRUG THERAPY

Drug treatments for osteoporosis may be broadly categorized into those which are directed at the prevention of bone loss, and those which are aimed at the augmentation of bone mass(8). The first group of drugs should ideally be imposed at the perimenopausal period before a substantial amount of bone has been lost. The latter drugs would be particularly useful in patients who have already lost much bone and who are thus at increased risk for skeletal fractures.

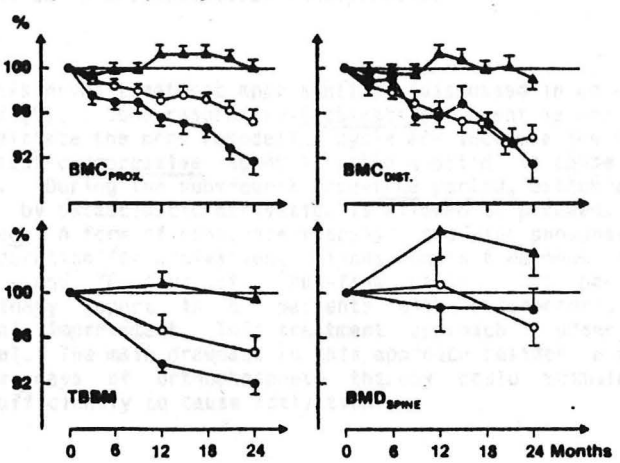
The first set of drugs may be called anti-resorptive medications (Fig. 1). They include currently available drugs: estrogen, calcitonin, and calcium supplements. Their principal mode of action is the inhibition of osteoclastic resorption. There may be a transient increase in bone mass due to this action. With continued treatment, however, a compensatory decline in bone formation ensues due to coupling. Thus, bone mass stabilizes; it does not continue to increase.

FIGURE 1. After Estelle & Riggs(8).



There is now convincing evidence that estrogen therapy is capable of preventing the loss of cortical and trabecular bone mass in women deficient in estrogen from natural menopause or surgical castration(2)(Fig. 2). A similar favorable response has been found with calcitonin. Both drugs may cause an initial increase in bone mass during the first 6-24 months. Thereafter, the bone mass remains stable without a further increase.

FIGURE 2. After Riis et al(2).



Bone-Mass Measurements in the Groups Treated with Percutaneous Estrogens (▲), Calcium (○), and Placebo (●).

Recent studies indicate that calcium carbonate supplementation may be ineffective in preventing spinal bone loss in early postmenopausal women. However, our own preliminary study suggests that calcium citrate supplementation may be effective in stabilizing vertebral bone mass. A randomized clinical trial of the comparison of two calcium salts, currently underway by the Dallas Area Osteoporosis Study and Management Group, may resolve this apparent discrepancy.

The second group of drugs may be called formation-stimulating medications, since they are directed at promoting osteoblastic bone formation in an effort to augment bone mass(8)(Fig. 1). These drugs are ideally suited for the management of established osteoporosis. While no drugs have been approved for this purpose in the United States, several investigational approaches hold promise. They are: exogenous PTH, coherence therapy (ADFR or activation-depression-free-repeat), and sodium fluoride.

PTH

Parathyroid hormone could theoretically increase bone mass by raising the number of bone multi-cellular units (BMUs) and by creating a net positive balance of each BMU. This concept was previously discussed in an earlier Medical Grand Round(9). Previous studies disclosed that the treatment with human PTH 1-34 peptide increased trabecular bone mass in osteoporotic women(10). However, this beneficial event may have occurred at the expense of cortical bone. There is some evidence that a sequential treatment with PTH followed by 1,25-dihydroxyvitamin D may overcome this "steal" syndrome (redistribution of trabecular and cortical fractions). In male patients with idiopathic osteoporosis, this sequential treatment has been shown to significantly increase the mass of trabecular bone of the spine without altering radial (cortical) bone mass(11). This approach has not been tested in postmenopausal osteoporosis.

ADFR

In this novel treatment approach(12) (discussed in an earlier Medical Grand Round)(9), a bone resorptive (activating) agent is applied first in order to initiate the bone remodeling cycle and increase the number of BMUs. An osteoclastic depressive agent is then applied to cause cessation of resorption. During the subsequent drug-free period, osteoblastic formation stimulated by osteoclastic activation is allowed to proceed. This sequence is repeated. A form of coherence therapy, involving phosphate treatment of 3-days' duration for activation, diphosphonate treatment of 15 days for depression and 70 days of drug-free period, has been tested(13). A preliminary report in 5 patients with osteoporosis disclosed a histological improvement. This treatment approach is undergoing a multi-clinic trial. The main drawback to this approach resides in the reservation that three days of orthophosphate therapy could stimulate parathyroid function sufficiently to cause activation.

Fluoride

The principal action of fluoride on the skeleton is the promotion of appositional bone growth on existing surfaces from the stimulation of osteo-

blastic formation(14). There is recent evidence, however, that fluoride may cause focal osteoclastic resorption. Thus, fluoride treatment could allow remodeling of bone and increase the number of BMUs.

There is extensive literature concerning the action of fluoride on the skeleton. The evidence that fluoride could augment bone mass, particularly of the trabecular bone, is convincing. Numerous studies indicate that fluoride treatment appropriately applied could augment bone mass and inhibit fractures in osteoporosis(15,16). It has been proclaimed by Baylink as the "single most effective agent" for osteoporosis(17). However, several problems have kept this drug from approval by the FDA; they include: frequent gastrointestinal and rheumatic complications, non-responsiveness in some patients, and the concern that it may cause the formation of a mechanically defective bone(15).

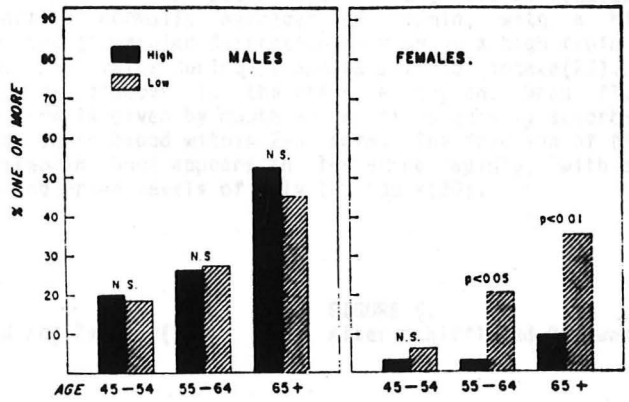
There is emerging evidence, particularly from our laboratory, which indicates that these problems could be overcome. This expectation is the basis for the devotion of the remainder of this Medical Grand Round to the consideration of the role of fluoride in osteoporosis. After a brief discussion of historical background, I shall review this topic 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.

THE ROLE OF FLUORIDE IN OSTEOPOROSIS

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 in India and elsewhere. More recently, several epidemiological studies disclosed that fluoridation of domestic drinking water may protect against the development of osteoporosis. Leone et al(18) found a reduced occurrence of vertebral osteoporosis in Bartlett County, Texas with a fluoride content in drinking water of 8 mg/liter compared to that in Farmington, Massachusetts with a fluoride content of the drinking water of 0.09 mg/liter. Bernstein et al(19) 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 (Fig. 3). However, the subjects in the fluoridated area also had a history of high consumption of dairy products. Similarly, Simonen and Laitinen(20) 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(21). Sowers et al(22) found 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.

FIGURE 3. After Bernstein et al(19).



Percentage of one or more collapsed vertebrae in subjects from high- and low-fluoride areas.

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

The dietary content of fluoride is normally low(23). Certain foods, such as tea and rice, are high in fluoride.

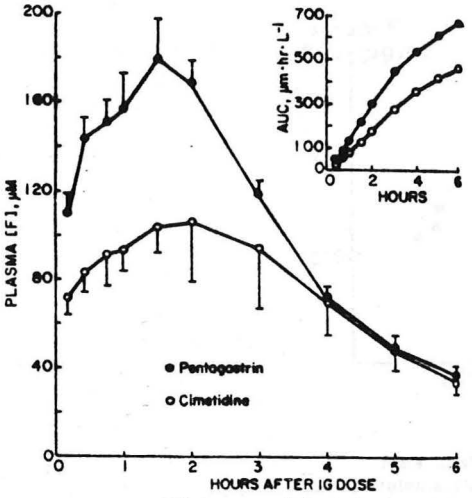
Intestinal Absorption of Fluoride

Fluoride absorption from the intestinal tract occurs passively; there is no evidence for active transport(23). Absorption of fluoride occurs largely in its undissociated form (hydrofluoric acid)(24). 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 (Fig. 4). It is also impeded following ingestion of milk(25) or calcium(26) due to formation of calcium fluoride of low aqueous solubility. No homeostatic regulation for fluoride absorption has been recognized(27).

Renal Handling

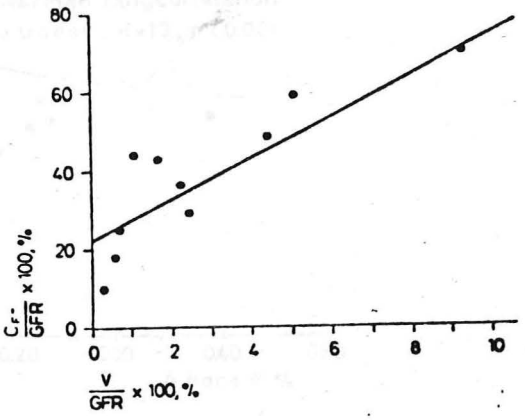
Fluoride is freely filtered in the kidneys. Some of the filtered fluoride is reclaimed by tubular-back diffusion. Thus, there is a close correspondence of filtered water and urinary fluoride(28,29)(Fig. 5). Fluoride clearance normally averages 65 ml/min, with a higher value approximating the glomerular filtration rate under a high fluid intake, and falling below this value during inadequate fluid intake(29). 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 hours. 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 hours(30).

FIGURE 4.
After Whitford and Pashley(24).



Time courses of plasma fluoride concentrations and cumulative AUCs in rats pretreated with pentagastrin or cimetidine. The fluoride dose, 5.0 mg/kg i.g., was given at t = 0.

FIGURE 5.
After Schiffl and Binswanger(28).

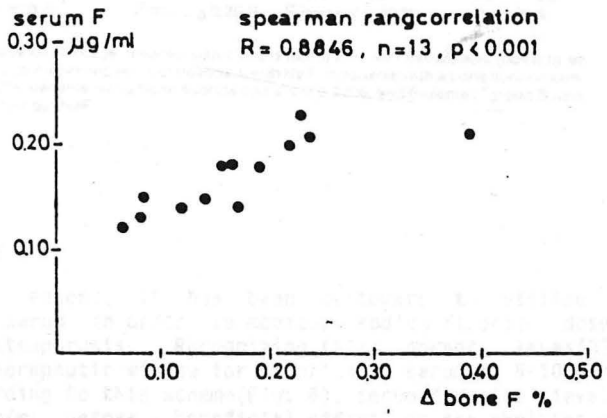


Correlation between the fractional excretion of filtered water and fluoride. C_{F^-} = renal clearance of fluoride; V = urinary flow rate; GFR = glomerular filtration rate. $y = 21.96 + 5.84x$; $r = 0.87$; $p < 0.01$.

Fluoride Uptake by Bone

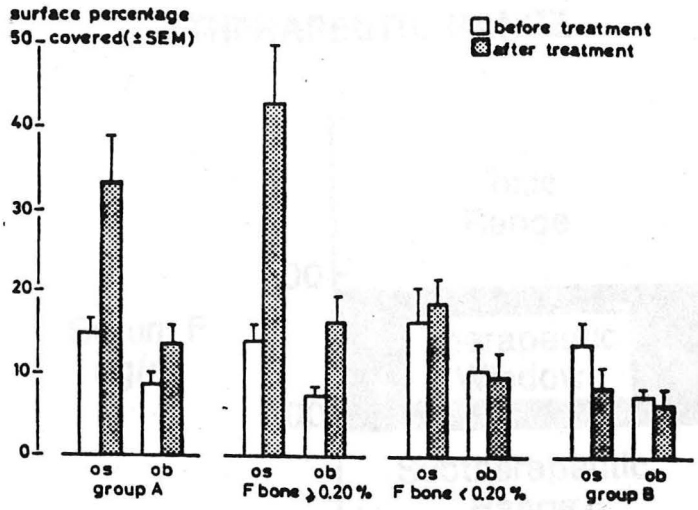
Within the first 3 months of fluoride therapy, approximately 50% of absorbed fluoride is deposited in bone, the remainder appearing in urine(23). After bone becomes saturated, absorbed fluoride largely appears in urine. Data on skeletal fluoride content following fluoride therapy are sparse because of the requirement for bone biopsy. While a preliminary report indicated that skeletal fluoride content may be assessed by NMR(31), further refinement and quantitation are required. Nevertheless, available data suggest that serum fluoride level provides a reflection of skeletal fluoride content(32)(Fig. 6). Moreover, the skeletal fluoride content correlates with the expected histomorphometric changes of fluoride in bone(32)(Fig. 7).

FIGURE 6. After van Kesteren et al (32).



Relationship between the mean fasting serum fluoride concentrations, during the whole period of treatment with NaF, and the increase in bone fluoride content after two years.

FIGURE 7. After van Kesteren et al(32).



Surface percentage covered with osteoid (os%) and with osteoblasts (ob%) in all patients of group A after two years of treatment with NaF, in patients with a bone fluoride content of ≥0.20%, patients with a bone fluoride content <0.20%, and patients of group B who were treated without NaF.

Therapeutic Window

For above reasons, 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(33) first established the therapeutic window for fluoride in serum at 5-10 µmolar (95-195 ng/ml). According to this scheme(Fig. 8), 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(34). 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 reported that skeletal calcium content increased when serum fluoride level was kept between 72-165 ng/ml, whereas it decreased when serum fluoride level was kept below 91 ng/ml(35)(Table 1).

FIGURE 8

THERAPEUTIC RANGE

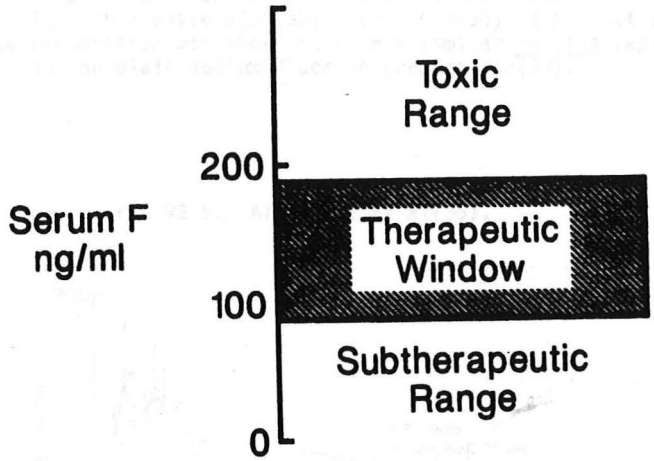


TABLE 1

DEPENDENCE OF SKELETAL RESPONSE ON SERUM FLUORIDE LEVEL

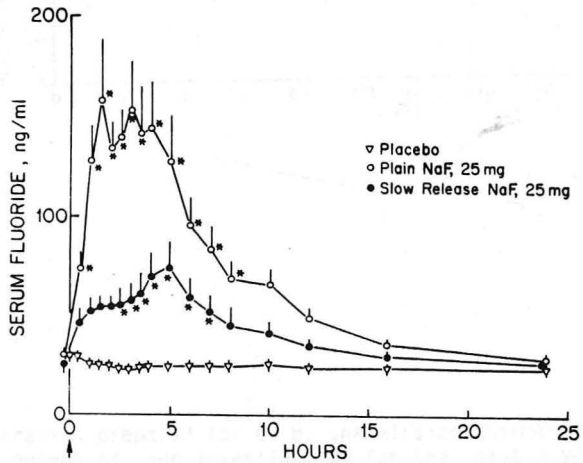
	Fluoride Retention	
	Adequate	Inadequate
Serum F, ng/ml	72-165	46-91
Bone F (F:Ca, mg/g)	14.2-28.0	8.1-10.1
Δ CaBI x 100	+12.7	-7.2

After: Harrison et al., JCEM 52:751, 1981

Bioavailability of Different Sodium Fluoride Preparations

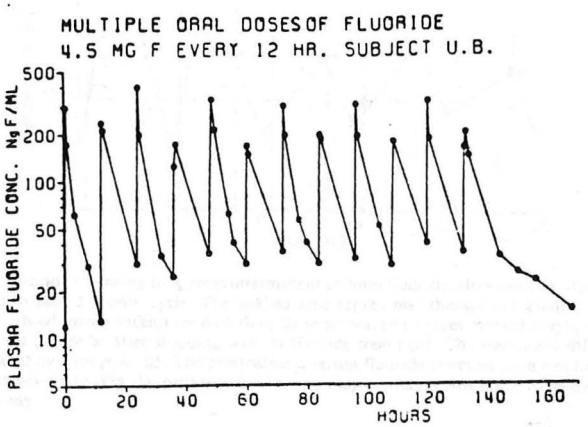
Following administration of a plain sodium fluoride preparation, serum fluoride level reaches a sharp peak rapidly(36)(Fig. 9), reflecting optimum absorbability of undissociated sodium fluoride. Thereafter, serum fluoride rapidly declines to the basal level within 12 hours. Thus, twice daily administration 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(37)(Fig. 10). The delivery of fluoride in an enteric coated form or as an organofluoride does not appear to substantially alter this pattern(38,39). In one study, a product labeled as a slow-release preparation was shown to have a similar in vivo rapid-release characteristic as the plain sodium fluoride preparation(39).

FIGURE 9. After Pak et al(36).



Fluoride bioavailability in 8 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 $p < .05$. Mean and SEM are shown.

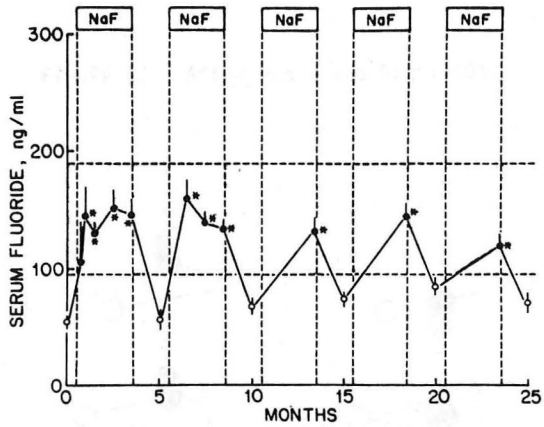
FIGURE 10. After Ekstrand et al(36).



Slow-Fluoride

The preparation prepared for us by the Mission Pharmacal Co. and which has been the object of our investigation for the past 5 years appears to satisfy the slow-release characteristic. Following its oral administration, serum fluoride concentration rises more slowly, reaching a peak at about 4-5 hours, reflecting absorption of fluoride anion distal to the stomach(36)(Fig. 9). Therefore, it declines slowly, maintaining a value above the basal level even at 12 hours. 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(36)(Fig. 11). This property may be critical in assuring safety of usage and in obviating formation of mechanically defective bone (to be discussed).

FIGURE 11. After Pak et al(36)



Fasting serum fluoride following long-term intermittent sodium fluoride (slow-release) therapy. Sodium fluoride was given for 3 months in each 5-month cycle. The shaded area represents "therapeutic window," enclosing threshold therapeutic level and threshold toxic concentration of fluoride in serum. (●) Values derived during sodium fluoride treatment; (○) values obtained before or after stopping sodium fluoride treatment. The significant difference from the pretreatment value is indicated by * for $p < .05$. The pretreatment serum fluoride concentration was higher than that for the acute fluoride bioavailability study (Fig. 1), probably because no major attempt was made to restrict normal fluoride intake in the long-term study.

PHYSICOCHEMISTRY

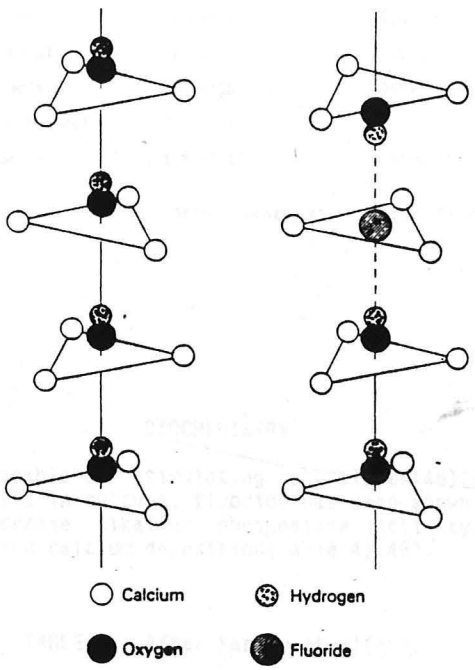
The physicochemical effect of fluoride on the skeleton is well known. The reaction of fluoride with hydroxyapatite of the bone mineral results in the formation of fluoroapatite from the substitution of hydroxyl ions by fluoride ions(40)(Fig. 12). Fluoroapatite is more crystalline(40) and has a larger crystalline size and lower solubility than hydroxyapatite(41)(Table 2). Bone powder from fluoride-treated animals has a preponderance of higher density fractions than from untreated animals(42). Partly owing to these physicochemical properties, the fluoride-treated bone is less subject to dissolution(43).

TABLE 2.

SOLUBILITY OF BONE MINERAL

	Solubility Products pK
$Ca_{10}(OH)_2(PO_4)_6$	54.6
$Ca_{10}F_2(PO_4)_6$	59.7
$CaHPO_4 \cdot 2H_2O$	6.6
CaF_2	10.4
$Ca_3(PO_4)_2$	28.9

FIGURE 12. After Hanes and Reddi(40).



PHYSIOLOGICAL ACTIONS OF FLUORIDE

During long-term treatment with fluoride, no change in intestinal calcium absorption has been observed(44). However, a decline in urinary calcium excretion has been noted(44), a finding attributed to the skeletal retention of calcium produced by fluoride.

No significant change in serum calcium or phosphorus has been reported(45)(Table 3). Serum immunoreactive PTH is typically normal when fluoride is given with an adequate amount of calcium or vitamin D. A rise in urinary nondialyzable hydroxyproline(45) and in serum osteocalcin concentration(36) may occur, indicative of osteoblastic stimulation. At high doses of fluoride, serum alkaline phosphatase may increase(17).

TABLE 3.

PHYSIOLOGICAL ACTION OF FLUORIDE THERAPY

	Placebo	NaF
Patient No.	20	20
Serum Ca, mg/dl	9.8±0.7	9.8±0.5
P, mg/dl	2.7±0.5	2.9±0.5
PTH, pg/ml	347±150	367±159
Urinary ND-OH-Prol µg/mg Cr	1.51±0.45	2.05±0.72*

After: Manzke et al, Metab. 26:1005, 1977

BIOCHEMISTRY

Fluoride is capable of stimulating osteoblasts(46)(47). 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(Table 4)(46).

TABLE 4. After Farley et al(46).

Parameter tested	NaF		Effect (percent of control)	*P*
	Concentration (μM)	Exposure (hours)		
	Cells			
[^{3}H]Thymidine incorporation	10	18	163 ± 14	< 0.005
Cell number	10	36	162 ± 17	< 0.005
ALP activity	10	144	435 ± 33	< 0.001
	Bones			
[^{3}H]Thymidine incorporation	25	72	146 ± 10	< 0.01
ALP activity	2.5	144	156 ± 14	< 0.01
^{45}Ca deposition	2.5	144	131 ± 6	< 0.002
[^{3}H]Hydroxyproline incorporation	2.5	144	152 ± 14	< 0.01

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(48). Thus, increased adenyl cyclase activity has been shown in isolated bone cells(49) following fluoride exposure, and the tissue content of cyclic AMP in bone has been shown to be raised after fluoride therapy(50)(Table 5). In addition, fluoride has been shown to inhibit Mg, Ca-ATPase in cultured osteoblast-like cells(51). 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 was shown to inhibit phosphotyrosyl phosphatase of osteoblasts(52). The resulting rise in intracellular levels of phosphotyrosine could then lead to stimulated osteoblast proliferation.

TABLE 5.

EFFECT OF FLUORIDE ON ADENYL CYCLASE OF ISOLATED BONE CELLS

	Adenyl Cyclase Activity (pmoles cAMP/mg protein/min)
Control	169±13
NaF, 10mM	1001±38^{+}

After: Kohler et al, Calc. Tissue Int. 36:279, 1984

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(15). Histomorphometric analysis of bone has disclosed that both bone formation rate and resorption rate are reduced at each BMU, indicative of toxic effect on bone cells(53)(Table 6). Following long-term exposure to fluoride, the amount of osteoid surfaces covered by osteoblasts are decreased, suggestive of reduced osteoblastic activity(15). Moreover, fluoride therapy at a high dosage has been shown to be associated with the synthesis of collagen with defective cross-linking(54), and with an over-production of dermatan sulfate, an inhibitor of calcification(55-57). These effects may cause impaired mineralization of bone.

TABLE 6.

TOXIC EFFECT OF FLUORIDE ON BONE CELLS

	Spayed Beagles	Fluoride-exposed Beagles
Index of activation foci/yr	176.4	557.6*
Bone formation rate/BMU $mm^3/mm^2 \times yr$	2.17	1.06
Bone resorption rate/BMU $mm^3/mm^2 \times yr$	6.89	0.59

After: Snow & Anderson, Calc. Tissue Int. 38:217, 1986

These findings emphasize the need to provide fluoride in a form 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 bone growth on existing surfaces(8,58). Thus, it is capable of increasing the thickness of existing trabeculae(59).

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(60,61). 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 (non-mineralized 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 (Table 7)(62-64). 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(65). However, approximately 15% of patients may show mild osteomalacia and 25% of patients may not show any histological response(62).

TABLE 7. After Meunier et al(62).

Changes in mean values for histological variables after 2 years of combined therapy NaF-Ca-Vit D (females).

	TBV (%)	TOS (%)	TIOS	TORS (%)	Cr (μm/day)
Pretreatment	9.9 ± 3.8	20.7 ± 9.9	14.5 ± 7	5.3 ± 2.7	.59 ± .19
Posttreatment	15.9 ± 8.6	50.7 ± 20.6	19.2 ± 7.9	5.8 ± 3.2	.52 ± .22
n	29	37	37	34	40
p <	.001	.001	.02	NS	NS

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(66).

EFFECT OF FLUORIDE TREATMENT ON BONE MASS

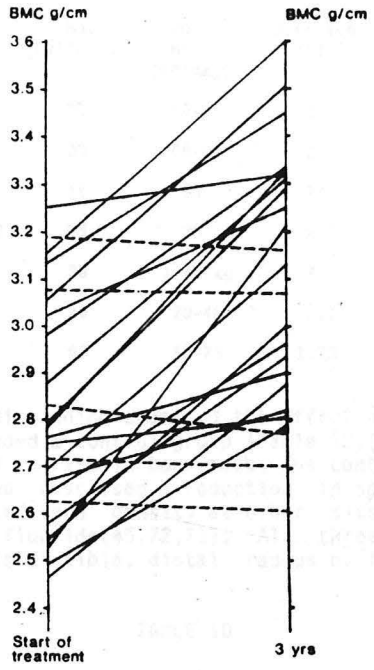
There are six studies which examined the effect of long-term fluoride treatment on spinal bone mass (Table 8)(35,67-70). The dose of sodium fluoride varied from 30-80 mg/day, and the duration of treatment ranged from 1.23 to 3 years per patient. One study measured total skeletal calcium content (CaBI) by neutron activation(35). Three studies assessed bone mass by dual photon absorptiometry (DPA) and two studies by quantitative CT. All six studies reported an increase in spinal bone mass, ranging from 2.9-23.5% per patient/year (Fig. 13). 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.

TABLE 8.

EFFECT OF FLUORIDE TREATMENT ON SPINAL BONE MASS

Authors	No. Patients	Dose NaF (mg/day)	Duration (yr)	Method	Change (%) Total	Per Yr.
Harrison et al (1981)	8	50	3	CaBI	12.7	4.2
Raymakers et al (1987)	53	50-75	1.23	DPA	3.6	2.9
Hansson and Roos (1987)	24	30	3	DPA	17.0	5.7
Duursma et al (1987)	13	40-80	2	CT	47.0	23.5
Healey et al (1988)	90	1 mg/kg	?	CT	?	9.0
Pak et al (1988)	21	50	2.9	DPA	11.8	4.1
Combined	209				13.1	7.3

FIGURE 13. After Hansson and Roos(68).



The individual changes in BMC in group A during 3 years' treatment with 30 mg NaF and calcium. The dotted lines represent the 5 subjects who did not respond to this treatment.

In contrast, fluoride treatment had a variable effect on the bone mass at other sites (Table 9)(45,67,70-73). The bone mass of the mataphysis or diaphysis of long bones increased slightly during fluoride treatment, except in one study(73) 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.

TABLE 9.

EFFECT OF FLUORIDE ON BONE MASS AT OTHER SITES

Authors	No. Patients	Dose NaF (mg/day)	Duration (Yr)	Site	Change (%) Total	per Yr
Farley et al (1987)	30	66-95	2	Distal radius	2.0	1.0
Farley et al (1987)	30	66-95	2	Radial shaft	2.0	1.0
Dambacher et al (1986)	15	80	2	Distal tibia	1.0	0.5
Christiansen et al (1980)	25	20	2	Distal radius	-3.6	-1.2
Healey et al (1988)	90	1 mg/kg	?	Femoral neck	?	4.5
Manzke et al (1977)	20	20-40	2.1	Finger	-0.14	-0.07
Raymaker et al (1987)	53	50-75	1.23	Femoral neck	-0.66	-0.54

Three of the studies which examined the effect of fluoride treatment on spinal bone mass included a control group (Table 10)(35,67,68). 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(45,72,73). All three showed a reduction in bone mass of the distal tibia, distal radius or finger without fluoride treatment.

TABLE 10

CHANGES IN BONE MASS IN THE CONTROL GROUP

Authors	No. Patients	Duration (Yr)	Site	Method	Change (%) Total	Per Yr
Harrison et al (1981)	6	3	Spine	CaBI	2.1	0.7
Raymaker et al (1987)	18	1.11	Spine	DPA	-1.68	-1.51
Hansson and Roos (1987)	19	3	Spine	DPA	-0.03	-0.01
Dambacher et al (1986)	14	2	Distal tibia	CT	-6.6	-3.3
Christiansen at al (1980)	103	2	Distal radius	SPA	-3.3	-1.7
Manzke et al (1977)	20	2.1	Finger	X-ray	-5.2	-2.5
Combined	**180**				**-3.09**	**-1.36**

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-Fluoride was comparable to that reported by two other studies using DPA (Table 8).

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 (Fig. 14). The fracture load per area of human vertebra, reflective of resistance against compressive force, was shown to be substantially increased in fluorotic bone compared to control bone (Table 11)(74). In immobilized rat vertebra, the breaking strength indicative of resistance against compressive force, was substantially increased when rats were treated with fluoride, particularly with calcium(75)(Table 12). These results indicated that fluoride produces increased resistance to compressive forces, possibly by augmenting the total mass of bone.

FIGURE 14.

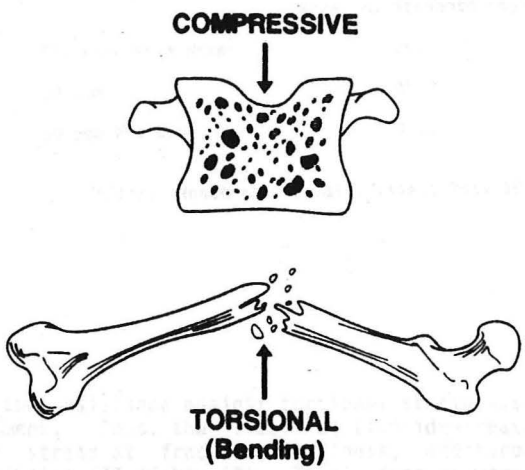


TABLE 11.

MECHANICAL PROPERTIES OF HUMAN VERTEBRA (COMPRESSIVE)

	Fracture Load/Area kp/cm^2
Control Bone 1	46.7
2	25.8
3	41.9
Fluorotic Bone	124.0

After: Franke et al, Acta Orthop. Scand. 47:20, 1976

TABLE 12.

MECHANICAL PROPERTIES OF RAT VERTEBRA (IMMOBILIZED)
(COMPRESSIVE FORCE)

	Breaking Strength (kg)
Fluoride Free Water	26.8
50 ppm F	35.0
50 ppm F + Ca	36.1

After: Rosen et al, Calc. Tissue Res. 19:9, 1975

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(76)(Table 13). These changes were much less marked when animals were fed fluoride with calcium(77).

TABLE 13.

MECHANICAL PROPERTIES OF RAT FEMUR (TORSIONAL STRAIN)

	Fluoride Level ppm		
	0	10	45
Group A (+Ca)			
Stress at Fracture (N/mm^2)	248	243	227
Flexibility ($1/Nmm^2 \times 10^5$)	1.98	2.17*	2.58*
Stiffness ($Nmm^2 \times 10^{-2}$)	517	463*	394*
Group B (-Ca)			
Stress at Fracture (N/mm^2)	142	121*	81*
Flexibility ($1/Nmm^2 \times 10^5$)	5.19	5.47	9.18*
Stiffness ($Nmm^2 \times 10^{-2}$)	195	186	113*

After: Beary, Anat. Rec. 164:305, 1969

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-Fluoride 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 14)(62,71,78-80). The dose of sodium fluoride ranged from 40-110 mg/day, and the duration of treatment ranged from 1.5 to 4.11 years/patient. In these studies, the fracture rate of the vertebra during treatment ranged from 50-304 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.

TABLE 14.

EFFECT OF FLUORIDE THERAPY ON VERTEBRAL FRACTURE

Authors	No. Patients	Dose NaF (mg/day)	Duration (Yr)	Fracture Rate (no/1000 pt yr)
Farley et al (1988)	18	66-110	2	50
Riggs et al (1982)	33	50-60	4.11	304
Lane et al (1984)	10	60	1.75	143
Power and Gay (1986)	25	40-60	1.5	230
Meunier et al (1984)	57	40-75	2.0	220
Pak et al (1988)	21	50	2.9	160
Combined	164			207

None of the above studies included a randomly-allocated placebo-controlled group. However, there are 4 studies in which a control group or a group taking no medication had been included (Table 15)(72,78,80). 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.

TABLE 15.

VERTEBRAL FRACTURE RATE IN THE CONTROL GROUP

Authors	No. Patients	Treatment	Duration	Fracture Rate (no/1000 pt yr)
Riggs et al (1982)	45	Placebo/none	2.0	834
Riggs et al (1982)	27	Calcium	3.7	419
Dambacher et al (1986)	12	None	3.0	420
Power and Gay (1986)	24	Calcium	4.5	250
Combined	108			554

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 (Table 14). This conclusion needs validation by a randomized placebo-controlled trial. Such a study is in progress at Rochester, Minnesota and at Detroit, Michigan. Data are not yet available.

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 16)(32,35,68,74,78,79,81-83). 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 6-50% 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 15-37%, for a mean of 29.0%.

TABLE 16.

ADVERSE REACTIONS TO SODIUM FLUORIDE

Authors	No. Patients	NaF Preparation	Gastro-intestinal (%)	Rheumatic (%)
Riggs et al (1982)	61	Plain	23.0	16.0
Hansson and Roos (1987)	24	Plain	21.0	?
van Kesteren et al (1982)	13	Plain	50.0	15.0
Franke et al (1974)	33	Plain	?	24.0
Kuntz et al (1984)	19	Plain	32.0	16.0
Lane et al (1984)	10	Plain	?	20.0
Hasling et al (1987)	163	Plain	25.0	37.0
Harrison et al (1981)	16	Plain	6.0	25.0
Briancon & Meunier (1981)	74	Coated	21.5	32.0
Combined	413		23.5	29.0

In 4 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 17)(69,72,84). 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.

TABLE 17.

ADVERSE REACTIONS TO SODIUM FLUORIDE

Authors	No. Patients	NaF Preparation	Gastro-Intestinal (%)	Rheumatic (%)
Lie et al (1982)	13	Slow-release	8.0	8.0
Dambacher et al (1986)	15	Slow-release	7.0	47.0
Duursma et al (1987)	56	Slow-release	?	27.0
Pak et al (1988)	64	Slow-release	6.0	7.9
Combined	148		6.4	19.1

It is now believed that the articular pain occurring during fluoride therapy is the result of microfractures(85,86). 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(87). In a recent study, however, compiled data from 5 sites did not disclose a higher rate of fracture of the proximal femur than in the untreated population(88). It was noteworthy that patients who sustained femoral neck fracture were often those who took a high dose of sodium fluoride (Tables 18,19)(88). 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-Fluoride suggests that avoidance of sharp toxic peaks of fluoride in serum may further be useful.

TABLE 18. After Riggs et al(88).

INCIDENCE OF HIP FRACTURES

Center	No. of hip fractures	Patient-years of treatment	Duration of treatment (yrs)	Incidence (%/yr)
A	0	364	4.7	0
B	6	158	1.3	3.8
C	3	181	3.4	1.7
D	6	284	2.4	2.1
E	2	104	2.2	1.9
Totals	17	1,095	2.6	1.6

TABLE 19. After Riggs et al(88)

INDIVIDUAL CHARACTERISTICS OF PATIENTS WITH HIP FRACTURES

Case (Center)	Age (yrs)	Dose of NaF (mg/day)	Duration of therapy (mos)
1 (B)	63	66	21
2 (B)	77	66	7
3 (B)	69	88	24
4 (B)	78	176	11
5 (B)	62	50	8
6 (B)	81	88	10
7 (C)	76	50	6[a]
8 (C)	82	50	26[b]
9 (C)	69	50	6
10 (D)	80	50-75	44
11 (D)	71	52-66	5
12 (D)	74	60	28
13 (D)	76	60	5
14 (D)	77	45	9
15 (D)	79	45	20
16 (E)	75	50	10
17 (E)	77	50	21

[a]Fracture occurred during 6-month off-treatment period.
[b]Bone biopsy did not show osteomalacia.

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(89,90). 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(91). 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(92).

Fluoride has been shown to reduce the deposition of calcium in the kidneys in the animals fed a nephrocalcinogenic diet(93)(Table 20). It is noteworthy that Bernstein et al found reduced prevalence of aortic calcification among subjects living in areas in which the drinking water had been fluoridated(19). The mechanism for the apparent inhibition of soft-tissue calcification by fluoride remains obscure.

TABLE 20.

KIDNEY CALCIUM IN RATS FED FOR 4 WEEKS WITH NEPHROCALCINOGENIC DIET + NaF IN DRINKING WATER

NaF mmol/L	Kidney wet wt (g)	Kidney Ca µmol/g
0	1.12±0.07	116±21
0.6	0.91±0.06	104±22
1.2	0.86±0.09	14±2*
2.4	0.85±0.06	18±4*
3.6	0.85±0.04	11±1*
4.8	0.87±0.03	23±1*

After: Harrison et al, Clin. Biochem. 18:109, 1985

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 use a slow-release preparation of sodium fluoride combined with an optimally bioavailable calcium supplement. This conviction

investigation and is the basis for our multi-clinic trial currently conducted by the Dallas Area Osteoporosis Study and Management Group.

Using Slow-Fluoride, 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, gastro-intestinal 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 was lamellar in appearance, adequately mineralized, and was 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 non-compliance or subnormal dosage.

These preliminary potentially important findings need validation from the multi-clinic trial.

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