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FLUORIDES AND OSTEOPOROSIS

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The drinking water in many parts of the globe is so naturally rich in fluoride that local inhabitants develop endemic fluorosis (85). This condition is manifest clinically by a crippling bone and joint disease and by staining, mottling, and pitting of the teeth. Studies of this phenomenon led to the realization that fluoride has important biologic effects that "harden" mineralized tissues. Several attempts have been made to harness these properties of fluoride to improve bones and teeth that may be more brittle than normal. The most widely known and established of these programs has been the dental application of fluoride (topically, in mouth rinses, and water fluoridation programs) with a well-demonstrated decrease in the rate of caries development (17). Less well established is a thirty-year program of research aimed at strengthening the skeleton in the most common brittle bone disease, osteoporosis. In this chapter we review what is known about the biologic effects of fluoride on skeletal metabolism and skeletal histology and the clinical effects of fluoride therapy on bone mass and the prevention of fractures in osteoporosis.

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METABOLISM OF FLUORIDE

Fluoride is an important trace element in humans. After oral ingestion of fluoride salts, the absorption from the gut is almost 100% (18). About 50% of the ion is excreted by the kidney and the remainder is stored in bone. Serum levels of fluoride in normals and untreated osteoporotic subjects are approximately 0.06 mg per liter. During treatment of osteoporosis serum fluoride levels between 0.10 and 0.25 mg per liter have been regarded as optimal by several authors (31, 61, 62, 91) following the recommendations by Taves (86, 87). However critical review of publications by Taves highlights the limited data upon which these recommendations were based, and the so-called "therapeutic window" for serum concentration of fluoride has been demonstrated to be an unreliable indicator for establishing the optimal fluoride dose on an individual basis (21).

As determined by ion-specific electrode analysis of normal human ilium, the bone fluoride content is 0.08 ± 0.05% of bone ash. Similar values are found in untreated osteoporotic subjects, whereas they are increased to 0.24 to 0.67% in patients treated with sodium fluoride. Bone fluoride content in subjects demonstrating typical features of skeletal fluorosis is in the 0.56 to 1.33% range (7). Linear increases in bone fluoride content without any plateau effect have been demonstrated over six years of therapy (3). Recently, electromicroprobe analysis has enabled researchers to demonstrate the topographic distribution of fluoride at the microscopical level. In a patient treated with high doses, fluoride was found in cancellous bone sites corresponding to the bone formed during the period of fluoride treatment (2).

EFFECT OF FLUORIDE ON SKELETAL HISTOLOGY

In this section we review the effects of sodium fluoride on bone histology as assessed in clinical studies, and the findings are then interpreted employing Frost's quantum concept of bone remodeling. According to this theory bone resorption and bone formation in the adult skeleton are temporally and spatially coupled events carried out by a specialized group of cells (BRU, bone remodeling unit). Briefly, a small segment of existing bone is removed by osteoclastic resorption, and within the cavity new bone is laid down by osteoblasts to repair the defect (63, 64). Histological evidence suggests that fluoride is capable of directly inducing formation of new bone along a quiescent bone surface, thereby bypassing the resorption-formation remodelling sequence (8, 57, 93). This ability to contribute to a positive skeletal balance makes fluoride a potentially therapeutic agent in osteopenic diseases such as osteoporosis. Morphological studies of bone biopsies have demon-

strated that the predominant effect of fluoride therapy on the skeleton is osteoblastic stimulation (75, 91). In vitro studies have shown that fluoride stimulates the proliferation of human osteoblastic cells (54), and it has been proposed that fluoride may act as a mitogen by inhibiting osteoblastic acid phosphatase/phosphotyrosyl protein phosphatase activity, with subsequent stimulation of cell proliferation (47).

Bone produced under fluoride administration is defective both in its structure and its degree of mineralization. The specific morphological abnormality, termed "mottled bone," consists of an increased number of irregularly distributed osteocytes, lying in enlarged lacunae surrounded by halos of low mineral density. The bone matrix is irregularly fibrous and is "woven" rather than lamellar (68). Under fluorescence microscopy tetracycline labels appear diffuse and/or absent, resulting in the histologic picture of osteomalacia. The delayed and/or impaired mineralization of the newly formed bone matrix during fluoride therapy led to the realization that fluoride therapy must be accompanied by concomitant calcium supplementation (37, 38, 65). Calcium is also needed to suppress the secondary hyperparathyroidism and increased bone resorption that have been reported when fluoride is given alone (65). In fact, an inverse relationship between the amount of calcium and the extent of resorption surface has been shown in iliac bone samples (38). Vitamin D has been administered in combination with fluoride and calcium in many studies with the purpose of offsetting the delay in mineralization. However, the need for vitamin D supplementation has been questioned (13, 23, 59). The dose of fluoride is another important factor in determining the effects of fluoride on bone histology. In early studies doses from 10 to 200 mg per day of sodium fluoride were used (5, 45, 68, 74). Subsequently it was shown that the dose of sodium fluoride correlates positively with the extent of bone-forming surfaces: doses below 40 mg had no consistent effects, and doses above 80 mg impaired mineralization and caused mottled bone (38).

The above findings led investigators to recommend a combined therapeutic treatment regimen with a fluoride dose in the range of 40 to 80 mg per day. When combined therapy is used, histomorphometric studies have shown marked increases in the extent of the osteoid surfaces, increased mean osteoid thickness and osteoid volume, and thickening of the existing trabeculae, without significant changes in the extent of eroded surfaces. The lack of increase in bone resorption during fluoride treatment can be explained by the fact that fluoride treated bone is more resistant to mineral dissolution; this may be due to the improved crystallinity and reduced solubility of fluorapatite compared to hydroxyapatite. The possibility cannot be excluded, however, that endogenous fluoride released during bone resorption may have deleterious effects on the function of the osteoclasts, since many osteoclasts

have been seen in biopsy specimens without concurrent increase in the eroded surface (20). The imbalance between resorption and formation in favor of bone formation under fluoride treatment gives rise to a substantial increase in trabecular bone volume (1, 8, 23, 26, 46, 50, 55, 58, 59, 61, 67, 89, 91, 92, 93).

Histological response to sodium fluoride can be demonstrated after only two months of therapy in individual patients (45), and after six months by a more systematic evaluation of bone biopsies in groups of patients (13, 41, 42). In most studies the effects of sodium fluoride on bone histomorphometry have been assessed after a mean duration of one to two years of therapy. Whether a longer duration of treatment may be of major benefit to the patients is controversial. As compared to treatment for one to two years, no further gain in the amount of cancellous bone has been found when therapy is continued for approximately three (39) or five years (23). On the other hand, accurate estimation of dynamic indices of bone formation by double labeling with tetracycline has provided evidence that while the mineral apposition rate and bone formation rate are unchanged or increased after one to two years of treatment (8, 13, 38, 55, 93), continuous treatment for approximately three years leads to marked depression of bone formation rate and severe impairment of osteoblast vigor (39). Lower doses (40–60 mg per day) of sodium fluoride in combination with calcium phosphate and calciferol for approximately five years are also associated with reduced bone formation at the cell level and significant prolongation of the mineralization lag time, suggesting an inhibition of osteoblastic activity (23).

By contrast, Lundy et al (50) have suggested that prolonged continuous therapy with sodium fluoride (40–100 mg per day) does not cause progressive mineralization defect. They found qualitative and quantitative evidence of mineralization defect in 80% of the biopsies obtained after approximately three years of therapy. However, in biopsies taken 50 months later, osteomalacia was no longer apparent. Interestingly, in four patients who had stopped fluoride treatment prior to the second biopsy for periods varying from one to four years, no evidence of mineralization defect was present. The latter observation is at variance with the results of Franke & Halle (27), who observed relapses three to four years after the interruption of fluoride therapy. While Lundy's findings should be interpreted with caution because of the small number of biopsies analyzed and the lack of pretreatment biopsies, it is evident that information regarding long-term effects of fluoride on bone histology is missing.

An interesting feature of fluoride treatment is that response does not occur in all patients; the proportion of patients showing increase in bone-forming surfaces ranges from 55 to 75% (8, 9, 33). Evidence suggests that patients who develop histological effects of fluoride will eventually achieve greater

bone mass in the spine as measured by neutron activation analysis (21, 33). The histological profile prior to fluoride treatment cannot be used to ascertain whether the patient will respond to therapy or not (8, 9, 13), and it has been claimed that the bone fluoride content is the best predictor of response to treatment (8, 9, 13, 91).

When a combined therapy is used the accretion of new bone does not occur without abnormality of the bone matrix in some of the patients: Increased osteocyte cellularity and enlarged osteocyte lacunae indicative of fluoride cytotoxicity upon osteoblasts and/or osteocytes have been reported even after treatment for only 18–24 months with relatively low doses of sodium fluoride (40–60 mg per day) in combination with vitamin D and calcium (16, 93).

To avoid the development of osteomalacia it was proposed that a more effective regimen would be to give vitamin D and calcium alternately with fluoride rather than concurrently (41, 42). Various intermittent regimens have been adopted. Pak et al (62) used sodium fluoride in combination with vitamin D and calcium in cycles of three months followed by treatment with vitamin D and calcium for six weeks. Kleerekoper et al (42), gave sodium fluoride with calcium for six months followed by six months of calcium treatment alone. Duriez et al (16) used a combined (fluoride-vitamin D-Ca) treatment regimen in cycles of two months. The results of these studies are disappointing. In one study after completion of four cycles no significant increase in bone volume could be demonstrated (62). In another study a discontinuous treatment regimen did not offer any greater protection than that provided by continuous treatment with respect to the development of microradiographic signs of bone fluorosis (16). Lastly, comparison of changes in skeletal histology in a group of patients receiving intermittent therapy (for 28.2 ± 21.4 months, mean ± standard deviation) with changes in a group of patients receiving continuous therapy (for 10.8 ± 4.89 months, months ± standard deviation) failed to demonstrate any differences between the two treatment regimens (39).

An intriguing finding is that the development of bone fluorosis is clinically asymptomatic when fluoride is used therapeutically for osteoporosis. Therefore, whether histological fluorosis should be considered a pathological finding (detrimental effect) or a factor of therapeutic efficacy remains open to question. Osteoid accumulation and delayed mineralization may be a necessary stage for a satisfactory therapeutic response, since the same patients presenting histological osteomalacia also showed significant gain in mineralized bone volume (8). This latter characteristic differentiates the fluoride-induced osteomalacia from that occurring in vitamin D deficiency.

The effects of sodium fluoride on cortical bone have been the subject of a few studies (41, 44, 55). While there is convincing evidence that adults with osteofluorosis have increased cortical thickness in iliac bone biopsies (7, 88),

no significant changes have been found in osteoporotic subjects receiving therapeutic doses of fluoride (41, 44, 55). After combined treatment for six months, an increased number of Haversian systems undergoing remodeling led to a slight increase in cortical porosity; after five years a defect in bone mineralization was evident (44).

In conclusion, histological studies show that fluoride exerts anabolic effects on bone tissue. Despite differences in the studies reviewed, for example in the treatment regimen—particularly with respect to vitamin D supplementation, the results generally support the hypothesis that in patients with osteoporosis, fluoride uncouples bone remodeling. There is increase in bone mass and no significant changes in bone resorption indices. The absence of histological response to sodium fluoride has been proposed as a useful criterion to identify the proportion of patients who are not going to benefit from the treatment. Prolonged therapy with sodium fluoride will eventually result in histological osteomalacia. However, proof that the defect in mineralization may result in symptomatic osteomalacia rests on scanty isolated case reports (10, 28). Therefore, the clinical significance of the large accumulation of osteoid and delayed mineralization remains to be elucidated.

FLUORIDE THERAPY FOR OSTEOPOROSIS

Effects on Bone Mass

Sodium fluoride has been repeatedly shown to increase bone mineral density in the lumbar spine in at least 70% of patients receiving the drug (24, 25, 66). To our knowledge, only one formal dose response study of this effect has been carried out (32); this study demonstrated that 10 mg per day given with 1000 mg per day of calcium did not result in a significant increase in bone density over a three-year period. The only other dose tested was 30 mg per day (with 1000 mg calcium daily), which caused an annual increase in bone mass of approximately 3%. This increase was linear throughout the three years of therapy. Riggs et al (72) gave 75 mg per day of sodium fluoride with 1500 mg per day of supplemental calcium; using the same method for bone mass measurement as Hansson & Roos, they demonstrated an annual increase in spinal bone mass of approximately 9%. Again, this increase was linear over the four years during which sodium fluoride was administered. Several other groups have given sodium fluoride in doses of 40–50 mg per day with varying amounts of supplemental calcium and have monitored bone mass over two or more years, also using the same technique to monitor change. Figure 1, which is a composite of this data, shows the relationship between therapeutic dose of sodium fluoride and the change in spinal bone mass. Several assumptions can now be made about this dose response. Firstly, no diminution of the biologic effectiveness of sodium fluoride occurs for at least four years. Data of our

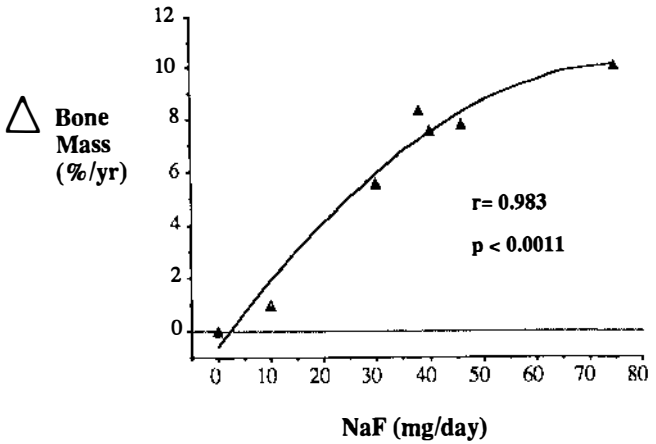

Figure 1 Dose response curve for fluoride and changes in bone mass per year. On the *horizontal axis* sodium fluoride dose in milligrams per day; on the *vertical axis* bone mass expressed as percentage change per year from baseline value.

own suggests that this may be true for periods as long as 10 years (40). We began using sodium fluoride as an investigational drug before we had the capacity to measure spinal bone mass. We were, however, able to demonstrate a significant linear relationship between spinal bone mass when first measured and the duration of therapy prior to that measurement ($r = 0.66$, $p < 0.0007$). Included in our study were some patients who had 10 years of therapy prior to the initial bone mass measurement.

This observation about the continued linearity of the bone mass response clearly distinguishes sodium fluoride from most, if not all, other potential therapies for osteoporosis in which the rate of increase in bone mass falls dramatically in the second and subsequent years of therapy (73). This observation also confirms that sodium fluoride cannot exert its effect on bone simply by inhibition of bone resorption as is the case with calcitonin and etidronate. Secondly, the therapeutic efficacy of doses above 75 mg per day is minimal, and doses below 30 mg per day would require very long periods of administration if therapy were to have a clinically important effect on bone mass. Patients who require an increase in bone mass <3% per year probably do not require any therapy at all. Thus, given the potential relationship between the dose of sodium fluoride and side effects (see below), the therapeutic dose of this drug is probably between 30 and 50 mg per day (approximately 0.5–0.75 mg/kg). Thirdly, formulation of the drug (plain, enteric-coated, slow release) does not appear to have much impact on the dose response curve. Additionally, an adequate dietary supply of calcium during sodium fluoride therapy (and any therapy aimed at increasing bone mass) is

required; the precise amount of supplemental calcium does not appear to be critical.

Finally, note that the dose response curve shown in Figure 1 underestimates the effect of sodium fluoride in increasing bone mass in the spine because the data is given for fluoride "responders" and "nonresponders." Most clinical studies of sodium fluoride in osteoporosis report that only 65–70% of patients respond with a significant increase in spinal bone mass. The reason(s) for failure of the therapy in some patients is unknown. It is unlikely to be a dose-related phenomenon, since the proportion of responders and nonresponders is quite similar in all studies even when different doses have been used. However, Hodsman & Drost (36) have demonstrated that nonresponders in their study ingested significantly less fluoride than responders, largely because the prescribed dose caused side effects of sufficient severity to limit patient tolerance of the medication. These investigators nonetheless concluded that it was not possible to segregate responders from nonresponders until 12–24 months of therapy had been completed. No difference between responders and nonresponders in the absorption of fluoride was observed, but the amount of fluoride incorporated into the skeleton was greater in responders (36). Attempts to identify responders on the basis of changes in biochemical markers of bone remodelling (e.g. serum alkaline phosphatase) have not yielded consistent results (19, 26).

The above discussion concerning the effect of sodium fluoride on bone mass relates only to bone mineral density in the lumbar spine and is probably generalizable to the axial skeleton; however, the effect of sodium fluoride on the appendicular skeleton is less clear cut. Two recently completed controlled clinical trials produced conflicting results concerning the effect of sodium fluoride on cortical bone mass in the forearm of patients with osteoporosis. One study demonstrated a greater rate of loss of cortical bone mass in the treated group compared to controls (72) while the other study showed no difference in the rate of loss between the two groups (43). Similar discrepancies have been reported from uncontrolled studies (15, 26, 36, 74). While reporting increased loss of cortical bone from the forearm, Riggs et al (72) did not demonstrate increased loss of bone from the proximal femur, a skeletal site with both cortical and cancellous bone. The few balance studies that have been completed suggest that sodium fluoride does not promote positive calcium balance even when spinal bone mass has been increased. These discrepancies in the reported effect on cortical bone mass and the lack of positive calcium balance have led some investigators to conclude that sodium fluoride increases spinal bone mass at the expense of appendicular bone mass. Furthermore, they speculate that if sodium fluoride can increase spinal bone mass to a level where the rate of vertebral fractures is reduced, this reduction

in vertebral fractures may be achieved at the cost of an increased rate of peripheral fractures. This important issue remains unresolved as discussed in more detail below.

Effect on Vertebral Fracture Rate (VFR)

A low bone mass is the most important determinant of the risk of sustaining a nontraumatic osteoporotic fracture. Therapies such as sodium fluoride that increase bone mass should, at least in theory, decrease the likelihood of fracture at sites where bone mass is increased; unfortunately, this hypothesis has proven extremely difficult to demonstrate. Only four prospective, placebo-controlled clinical trials of the anti-fracture efficacy of sodium fluoride have been completed during the thirty years of fluoride research (12, 43, 52, 72). Table 1 reports the overall results of these four trials, and one can see that sodium fluoride has no significant therapeutic advantage over placebo with respect to VFR. These observations are in sharp contrast to uncontrolled trials (8, 14, 52, 62, 71) that almost uniformly report a dramatic effect of the drug in reducing VFR. This discrepancy highlights the problems that have plagued osteoporosis research in general and fluoride research in particular. The natural history of vertebral fractures in an individual osteoporotic patient is impossible to predict but, generally, fractures tend to occur in clusters. Many patients thus enter clinical trials shortly after having sustained one or more new vertebral fractures and, even without intervention, might not be expected to sustain any further fractures for several years. Studies of the anti-fracture efficacy of sodium fluoride that do not include appropriate controls can therefore be disregarded for the most part. It can now be stated that sodium fluoride is no more effective than placebo in reducing the prospectively measured VFR in postmenopausal osteoporosis (49).

This is a disappointing observation, particularly since sodium fluoride is more effective than any other therapeutic agent currently in use or under investigation in terms of increasing spinal bone mass. The most plausible explanation is that the new bone formed under the influence of sodium fluoride therapy is "too little, too late." This is not a wholly satisfactory explanation because the absolute bone mass achieved in many fluoride-treated patients is well into the normal range and above the level where fractures might be expected to occur. It is likely that the newly formed bone, which can only be deposited on the architectural framework existing at the time therapy is begun, is not deposited in a site that improves the biomechanical competence of the skeleton even in the face of a "normalized" bone mass. The second plausible explanation is that the new bone formed under the influence of sodium fluoride is abnormal and that the induced abnormality imparts its own biomechanical incompetence to the skeleton.

Table 1 Vertebral fracture rates: sodium fluoride versus control

Source	NaF Dose (mg/d)	Control	Follow-up (years)	VFR per 1000 patient years	
				Control (n)	NaF(n)
Mamelle (52)	50	Various	2	640 (136)	480 (180)
Kleerekoper (43)	75	Calcium	2.5	529 (38)	733 (46)
Dambacher (12)	80	Placebo	3	417 (12)	1139 (12)
Riggs (72)	75	Calcium	3.5	525 (101)	462 (101)

Effect of Sodium Fluoride on Peripheral Fractures

In 1984 Gutteridge et al (31) reported anecdotally on a small group of osteoporotic patients who developed hip fractures while receiving sodium fluoride and concluded that the fractures had occurred as a side effect of the therapy. Subsequently, Riggs et al (70) reported that the hip fracture rate in a large number of women treated in five different centers in the United States and France was not different from that anticipated in an untreated osteoporotic population. This controversy remains unresolved today because of the paucity of properly conducted clinical trials. In none of the four controlled trials examining the effects of sodium fluoride on VFR (12, 43, 52, 72) was there a significant difference in the hip fracture rate between the control and treatment arms of the trials. However, it must be emphasized that the actual numbers of hip fractures in these studies was quite small and the mean age of the study subjects was generally less than the age where the incidence of hip fractures begins to rise appreciably. But anecdotal reports of hip fractures occurring in sodium fluoride–treated osteoporotic subjects still appear with some regularity (4, 30, 35). In contrast, Mackie et al (51) reported that 23 hip fracture patients treated with sodium fluoride fared better after 10 months of therapy than 23 untreated controls. Of the 23 treated patients 17 had improved amount and quality of cancellous bone and in 9 an increase in cortical thickness was noted.

This controversy surrounding sodium fluoride therapy and hip fractures has been fueled by the development of the "painful lower extremity syndrome" as a well-documented side effect of the therapy (11, 14, 22, 26, 27, 29, 32, 34–36, 56, 57, 69, 71, 76, 78, 80). This syndrome is manifest clinically by pain, tenderness, swelling, and occasionally redness of isolated regions of the lower extremity (heels and ankles > knees > hips). The lesions are seen almost exclusively in the lower extremity, indicating some association between load-bearing and sodium fluoride, and they occur at least three times more frequently in treated patients than controls. The lesions have many of the radiographic and scintigraphic features of "stress" fractures, leading many investigators to speculate that these are precursors of true fractures (77).

However few, if any, of these lesions have actually progressed to true fractures, so that the long-term clinical significance of the painful lower extremity syndrome remains unknown. Certainly in the short term the syndrome requires that the therapy be discontinued, and almost invariably the syndrome is healed clinically and radiographically within 6–8 weeks after stopping the drug. In many patients it is possible to reinstitute therapy without recurrence of the syndrome.

The etiology of this syndrome is unknown. It has been suggested that conditions like hyperthyroidism or inadequate calcium supplementation may favor its development (6, 48, 53). Schnitzler & Solomon (79) described two types of histologic lesions associated with sodium fluoride–induced calcaneal stress fractures. One feature was the presence of numerous large intratrabecular resorption cavities occupied by osteoclasts. They also described trabecular fissures that suggested healing microfractures. The surrounding newly formed woven bone was regarded as evidence of microcallus formation. Orcel et al (60) examined the histology of the ilium in 10 patients at the time they were experiencing stress fractures and demonstrated increases in osteoblastic and osteoclastic surfaces, an increase in osteoclast number, and large amounts of osteoid tissue. Bone fluoride content was high but not significantly greater than in patients who had not developed the syndrome.

Schultz et al (81–84) have postulated that the scintigraphic findings in fact represent a positive response to sodium fluoride therapy and indicate new bone formation rather than a side effect representing a fracture and subsequent repair. These investigators were able to demonstrate that those patients with the greatest occurrence of abnormalities on bone scan were in fact those with the greatest increase in spinal bone density. The histologic findings of Schnitzler & Solomon (79) and of Orcel et al (60) are not inconsistent with this hypothesis despite the marked difference in interpretation. Our own observations in a small number of patients failed to demonstrate a more frequent occurrence of the painful lower extremity syndrome in treated patients who did or did not develop histologic features of generalized osteomalacia while on sodium fluoride (unpublished observations). Our belief at present is that the syndrome is a definite side effect of sodium fluoride that warrants interruption of therapy but that the syndrome is short-lived and does not progress to true fracture. Further studies are clearly needed to clarify this point, particularly in light of the limited effect of sodium fluoride on peripheral bone mass even when there is a substantial increase in spinal bone mass. If it can be clearly demonstrated that spinal bone mass does indeed increase at the expense of peripheral bone mass (72), then it probably is just a matter of time before the incidence of hip fractures increases with sodium fluoride therapy. Such a finding would certainly provide further support for restricting

the use of sodium fluoride to properly conducted controlled clinical trials and would limit the potential benefit of therapy to those osteoporotic subjects already old enough to expect an increased likelihood of hip fracture even without sodium fluoride.

SUMMARY AND CONCLUSION

Sodium fluoride has clearly been shown to have pronounced effects on the skeleton, probably more than any other currently available therapeutic agent. Unfortunately, these effects appear to be both beneficial and potentially toxic at the same time. A more clear understanding is needed of the basic mechanisms whereby these effects (both beneficial and detrimental) are exerted. When such data are forthcoming, it may be possible to modify the therapeutic use of fluoride in osteoporosis and other brittle bone diseases such that the beneficial effects outweigh the toxic effects much more completely than is currently the case. Until such time, and despite thirty years of meaningful clinical investigation, we must conclude that sodium fluoride has no role in clinical medicine outside the confines of properly conducted clinical research studies.

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