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Fluoridation and Bone Disease in Renal Patients

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The question of whether fluoridation contributes to bone disease in patients with renal disease is an important one that deserves attention and further study. It is logical to be concerned about this possibility because of the important role of the kidney in the elimination of fluoride. However, the subject is extremely complicated for several reasons. Ever since the initial description of bony changes induced by fluoride in persons with normal renal function, there has been continuing controversy regarding whether these effects are harmful or beneficial (Johnson, 1965; Hodge and Smith, 1968; Jowsey, Riggs, and Kelly, 1978). Renal disease in itself produces additional complexities because of the effects of retained phosphate, depressed ionized calcium, excessive parathyroid hormone in the circulation, impaired formation of 1,25-dihydroxy D_3 by the diseased kidney, and impaired collagen synthesis, all of which adversely affect the integrity of the skeleton. The added significance of fluoride in this setting has been difficult to interpret (Rao and Friedman, 1975).

In the United States, there have been no reported cases of skeletal fluorosis in persons who drink water containing only one part per million (ppm) of fluoride. However, since no systematic studies have been carried out in patients with renal insufficiency, this possibility cannot be excluded with certainty. If it could be shown that no adverse effect occurred when the total intake of fluoride by patients with renal disease is higher than would be obtained by drinking fluoridated water with 1 ppm of fluoride, then one could assume that no adverse effect was occurring in the population.

There are two obvious settings in which patients with renal disease will receive more fluoride than would occur in normal subjects who drink fluoridated water. One of these situations occurs when patients with renal disease drink

serum levels that remain approximately the same as when they entered long-term dialysis therapy (Table 1). The bone content of fluoride is also greater in patients exposed to fluoridated dialysate than in those exposed to fluoride-free dialysate (Jowsey et al., 1972; Cordy et al., 1974). Whereas these findings are generally accepted, the specific effect of retained skeletal fluoride has been difficult to determine. Before proceeding with a description of patients with renal failure who were exposed to high concentrations of fluoride, it is appropriate to briefly describe the bone disease seen in patients with low fluoride levels.

Table 1. Serum fluoride concentrations.

Patient status	Concentration	
	µg/ml	µM
Normal (adults)	0.02	1.0
Chronic renal failure (Siddiqui et al., 1970)		
Serum creatinine <3 mg/dl	0.05	2.6
Serum creatinine >3 mg/dl	0.09	4.7
Hemodialysis (1 yr or more)		
Without fluoride (Jowsey et al., 1972; Cordy et al., 1974)	0.06	2.8 to 3.4
With fluoride	0.24	12.3 to 13.5

Bone Disease in Patients With Low Fluoride Levels

The changes in bone seen in patients with chronic renal insufficiency are complex in that there is a spectrum of findings. At one extreme is pure osteotis fibrosis, which shows a pattern of excessive bone resorption. This is seen histologically as excessive numbers of osteoclastic lacunae and reabsorption of bone by osteocytes. Roentgenographically, the bone has a moth-eaten appearance along subperiosteal surfaces. These changes are most easily seen in roentgenograms of the hands and of the distal portion of the clavicle.

At the other extreme is osteomalacic bone disease that is due to a deficiency of the active vitamin D metabolites normally produced by the kidneys. Osteomalacia is recognized histologically by excessive amounts of osteoid (that is, unmineralized bone matrix) and an increase in the fraction of the surface of bone that is forming bone matrix. Roentgenographically, the most easily recognized changes are narrow lines containing very little mineral (Looser zones). These lines probably represent actual fractures because they are frequently followed by callus formation similar to that seen in typical fractures. These two types of bone disease are,

of course, also seen in patients without renal disease. Patients with chronic renal disease often have a little of both types.

In addition, the patients occasionally have sclerosis. Histologically, the sclerosed bone exhibits an increase in the thickness of the trabeculae, and roentgenographically, there is a coarsening of the trabecular pattern with increased opacity of the mineralized tissues. Sclerosis and increased amounts of osteoid are also features of fluorosis. Therefore, Kaye and co-workers (1960) considered the possibility that these changes in patients with renal disease were due to fluoride exposure. They concluded, however, that this was not so because the bone fluoride concentration in their cases was considerably lower than that in reported cases of fluorosis. If this finding is correct and not just the result of failure to sample recently formed bone, then renal disease and fluoride cause similar changes. This overlap makes it very difficult to assess the effect of fluoride per se in these patients. Very large amounts of new periosteal bone and calcification of the interosseous ligaments are the only known features distinctive of fluoride, and these have not been noted in patients on hemodialysis (Johnson, 1965; Jolly, Singh, and Mathur, 1969).

Case Reports From High Fluoride Areas

Effects Prior to Dialysis

One case of symptomatic skeletal fluorosis (radiculomyelopathy) has been reported from an area in Texas with natural fluoride at 2.3-3.5 ppm in the water (Sauerbrunn et al.,1965). There have been two cases of suspected skeletal fluorosis (based on X-ray evidence) in the United States with fluoride at 2-3 ppm in the drinking water (Juncos and Donadio, 1972). The Department of Nephrology at the Mayo Clinic examines approximately 100 new patients with end-stage renal disease each year. Some of these patients reside in areas where the naturally occurring fluoride concentration in tap water exceeds 1 ppm. During the course of several years, six patients have been seen in whom fluoride may have been the cause of detectable clinical and roentgenographic effects. Two of these cases have been reported previously from our institution (Juncos and Donadio, 1972). One patient had chronic glomerulonephritis, and the others had congenital renal disease of more than 15 years' duration before skeletal symptoms developed (Table 2). Most of the patients had high urine volumes (>3 per day), the fluid being replaced by copious intake of water or in one instance, tea.

Table 2. Causes of renal failure in six patients exposed to high fluoride before dialysis.

Cause	No.
Congenital defects of bladder, ureters	3
Fanconi syndrome	1
Bilateral polycystic kidneys	1
Chronic glomerulonephritis	1

The most distinctive features suggesting fluorosis were the roentgenographic appearance of the skeleton and the severity of dental mottling (Table 3). The most characteristic roentgenographic finding was a diffuse increase in bone density which, in younger patients, assumed a ground-glass appearance; whereas in older patients, it showed a coarse trabecular pattern that became more obvious as the skeleton became more demineralized over the years and with progression of renal failure. In addition to the increase in bone density and the alteration of trabecular pattern, there was prominent new subperiosteal bone formation, especially in the long bones of the upper and lower extremities, and calcification of the interosseous ligaments between tibia and fibula and between radius and ulna, as well as of the sacrotuberous ligaments of the pelvis and the longitudinal ligaments of the spinal column in some of the patients. In addition, three patients had pseudofractures, a common feature of osteomalacia.

Table 3. Roentgenographic findings in six patients with renal failure who were exposed to high fluoride* before dialysis.

Finding	Patients
Increased bone density	6
Dental mottling	2
Calcified interosseus ligaments	2
Subperiosteal bone	2
Subperiosteal resorption	0
Fractures	3
Pseudofractures	3

*1.7 to 2.0 ppm.

Despite having severe symptomatic bone disease, none of the patients showed striking features of hyperparathyroidism, such as subperiosteal resorption or bone cysts, which, in the United States, are the more common manifestations of renal osteodystrophy. Plasma parathyroid hormone concentrations, although elevated in all of the patients, were relatively low considering the severity of the bone disease.

In addition, these patients developed severe skeletal changes or bone pain early in the course of renal failure when creatinine values were approximately 3 mg/dL. Symptoms

referable to the skeleton varied. Two of six patients were asymptomatic; four complained of arthralgia, especially of the knees, and of bone pain on weight-bearing involving the lower extremities; three of the patients had spontaneous fractures of metatarsals, ribs, and hip.

Bone biopsy specimens available from four patients showed a marked increase in the ratio of fluoride to calcium (Table 4). Biopsy specimens studied by quantitative microradiographic techniques showed a large percentage of bone surface covered by osteoid as well as thick osteoid seams with variable degrees of bone resorption and large areas of new bone formation.

Table 4. Patients exposed to fluoride prior to dialysis.

	Fluoride			Osteoid on bone biopsy	
Case	Water (ppm)	Serum (μM)	Bone* F/Ca	Surface (%)	Width (μM)†
1	1.9	14.1	5.9	65.3	42 ± 2.9
2	2.0	10.1	5.4	46.7	28.8 ± 3.8
3	1.7	5.0	3.5	45.2	21.9 ± 0.8
4	1.7	12.0	3.0	19.4	22.4 ± 2.6
Mean	1.83	10.3	4.4	44.2 ± 9.1	28.8 ± 4.6
Normal	1.0	1.7 ± 0.1	1.0	2.6 ± 0.6	14.3 ± 1.0

*Fluoride is expressed as molar percent relative to calcium.
†Mean ± SE.

Therapeutic measures included the elimination of fluoride from the drinking water, normalization of plasma calcium and phosphate concentrations, and the use of vitamin D analogs. Symptoms were lessened with these measures, but several patients continued to have fractures. Four patients have been free of symptoms or fractures since entering the dialysis program using fluoride-free dialysate and continuing efforts to maintain normal calcium and phosphate levels.

Case of Severest Disease. A 69-year-old man experienced excessive frequent urge to urinate associated with pyuria in 1958. Signs of infection cleared after sulfonamide therapy, but urinary frequency, nocturia, and polyuria persisted. The urine was of fixed specific gravity and showed a trace of protein. Mild azotemia appeared in 1960, followed by bone pain, arthralgia of the knees and feet, and spontaneous "march fractures" of both feet--a total of 13 by 1963.

Examination of the urine revealed no infection, but a 24-hour specimen showed an increased content of glucose and amino acid nitrogen. The urine was alkaline, while the blood showed some evidence of systemic acidosis. Blood sugar levels were normal, azotemia was mild, and alkaline

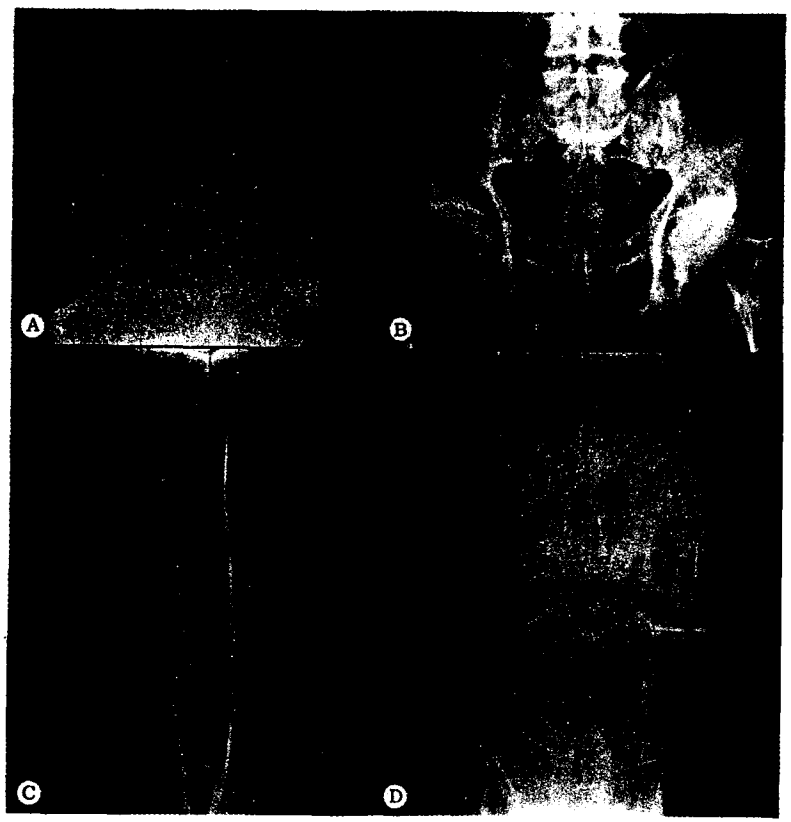

Fig. 1. A, Multiple healing fractures of metatarsals. Note increased bone density and coarse trabecular pattern. B, Increased density of pelvis, with coarse trabecular pattern and calcification of sacrotuberous ligaments. C, Calcification of interosseus ligament between radius and ulna. D, Coarse trabecular pattern and subperiosteal new bone formation of distal femur and proximal tibia.

phosphatase activity was elevated, but values for serum calcium, phosphate, and total protein were normal. An excretory urogram showed small kidneys. Skeletal roentgenograms showed healing fractures of the metatarsals and phalangeal bones of both feet, areas of increased bone density with a coarse trabecular pattern involving predominately the axial skeleton and calcification of interosseous ligaments, and new subperiosteal bone formation (Fig. 1).

Bone biopsy of the iliac crest showed an increase of uncalcified osteoid tissue on bone surfaces, decreased mineral density around osteocytes, low mineralization of cement lines, and much interstitium with an irregular pattern.

After treatment with oral calcium supplements and vitamin D, bone pain decreased but the patient experienced additional fractures. Osteosclerosis increased, but serum alkaline phosphatase values decreased to normal (Fig. 2). A bone biopsy specimen taken in 1968 showed healing of osteomalacia. Chemical values showed a high concentration of fluoride in serum (14 μM) and bone (4.7 to 6.5 moles of fluoride per 100 moles of calcium) and in drinking water (2 ppm or 106 μM) relative to the concentration of fluoride in the urine (78 μM).

At this point, the patient was advised to stop drinking tap water and to use only fluoride-free spring water or distilled water for both drinking and cooking. Serum fluoride concentrations decreased (to 8 μM), and for a period of approximately 8 years, the patient was relatively free of bone pain and did not experience further fractures.

In 1971, renal function temporarily deteriorated further. After peritoneal dialysis, renal function spontaneously improved. In 1974, the patient fell, sustaining a hip fracture that required internal fixation. Osteomalacia has persisted despite vitamin D therapy and reasonable control of systemic acidosis and secondary hyperparathyroidism. These findings were interpreted as representing adult Fanconi's syndrome with osteomalacia and superimposed fluorosis.

Effects of Fluoride in the Dialysate

Claims of Adverse Effects

After the introduction of home dialysis in 1964, several centers, including our own, noted a higher incidence of bone disease when patients used untreated or softened water to prepare the dialysate. One identifiable factor was the

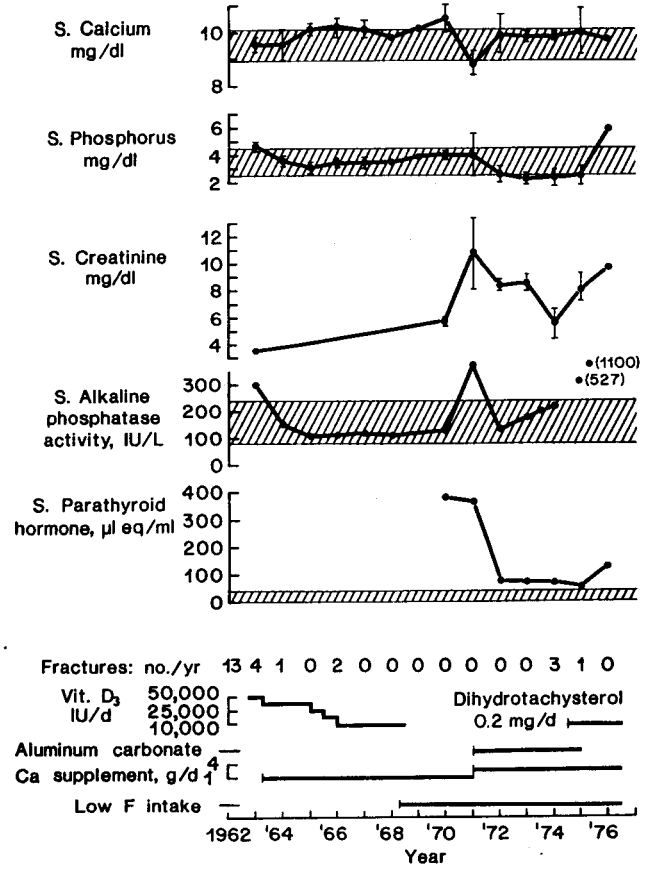

Fig. 2. Serum chemical values, clinical response, and treatment regimen in patient exposed to fluoride before dialysis. Hatched area = normal range.

presence of fluoride in water used at home but its absence in water used in the centers. Unlike the bone disease usually encountered in dialysis patients, these patients had little evidence of hyperparathyroidism, but, instead, had histologic evidence of severe osteomalacia. Five of the six patients exposed to fluoridated dialysate for an average of 23 months suffered bone pain and fractures, and three of these patients had incapacitating symptoms. Bone biopsy specimens from five patients exposed to fluoridated dialysate for more than 1 year were compared with those from six patients of approximately the same age, duration of azotemia, and duration of dialysis who were dialyzed using fluoride-free dialysate. The blood concentrations and ratios of bone fluoride to calcium were significantly higher in patients exposed to fluoridated dialysate (Table 5). Although the severity of osteitis fibrosis was similar in the two groups, as reflected by the percentage of bone surface undergoing osteoclastic resorption, osteomalacia was significantly more severe in the fluoridated group.

Table 5. Chemical and histologic features of patients exposed to low and high fluoride dialysate

	Dialysate F	
	<5µM (6 patients)	>50µM (5 patients)
Hemodialysis (mo)	22.0	20.0
Fluoride		
Dialysate (µM)	1.4	52.0
Serum (µM)*	2.8	13.2
Bone F/Ca*	1.0	3.2†
Osteoid surface (%)	3.0	27.5‡
Osteoid width (µM)	17.3	37.9†
Bone formation (%)	7.0	0.3
Bone resorption (%)	29.8	26.8

*Normal: In persons drinking water with a fluoride content of 1 ppm (53 µM), the serum fluoride is 0.7 ± 0.4 µM and the bone fluoride-to-calcium ratio, expressed as molar %, is 1.0, which is approximately 1,000 to 2,000 ppm on an ash weight basis.
Significant difference from <5 µM group: †$P<0.05$; ‡$P<0.01$.

Case of Severest Disease. A 46-year-old man with polycystic renal disease was maintained by long-term hemodialysis (Johnson and Taves, 1974). At first, a commercial water softener provided water containing 1 ppm of fluoride. The serum concentrations of calcium and magnesium were maintained in the normal or elevated range (tending to suppress parathyroid activity) and the serum phosphate values were never below normal and, therefore, were unlikely to induce

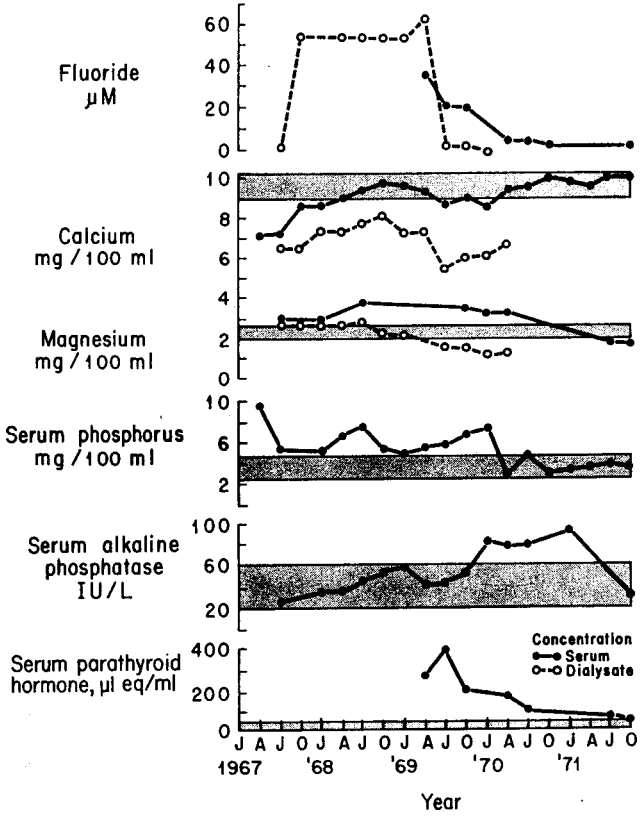

Fig. 3. Serum and dialysate chemical values from patient exposed to fluoridated dialysate and subsequently treated by renal transplantation. (From Johnson WJ, Taves DR. [1974] Exposure to excessive fluoride during hemodialysis. Kidney Int. 5;451-454. By permission of the International Society of Nephrology.)

phosphate-depletion osteomalacia (Fig. 3). Parathyroid hormone values also were below the average of patients on such a regimen.

Despite these measures, the alkaline phosphatase values increased steadily. Although initial skeletal surveys did not reveal abnormalities, within a year, the patient complained of chest pain and severe pain of the feet on weight-bearing. Examination of the skeleton showed generalized demineralization and fractures of three ribs, but no evidence of subperiosteal bone resorption. In spite of a good appetite and a seemingly adequate caloric and protein intake, the patient's weight decreased 11 kg.

Because we suspected that fluoride was implicated, a deionizer was recommended. Repeated determinations of dialysate fluoride, however, revealed variable values, some levels actually exceeding the concentration in tap water. Inspection of the apparatus revealed that, because the conductivity meter was defective, the patient had been using the water meter to determine when the deionizer required regeneration. Although this practice did not result in dangerous elevation of calcium and magnesium levels in the dialysate, fluoride was eluted from the column when the deionizer was exhausted. After correction of this problem, dialysate and serum fluoride concentrations decreased rapidly.

Bone biopsy specimens obtained before and after the reduction of serum fluoride levels showed a slight decrease in the ratio of bone fluoride to calcium from 3.4 to 3.0 and some improvement in the osteomalacia and bone resorption. Despite these encouraging findings, the patient did not improve clinically and at this point was bedridden because of bone pain and fractures. After nephrectomy and splenectomy in preparation for renal transplantation, he experienced a generalized seizure and suffered additional fractures of a rib, a lumbar vertebral body, and the right femoral neck.

After successful renal transplantation, serial skeletal roentgenograms and bone densitometry measurements showed remineralization and healing of fractures. During the next 6 years, the patient was free of skeletal complications. Values for serum calcium, phosphate, and alkaline phosphatase and parathyroid radioimmunoassay concentrations returned to normal, but serum fluoride concentrations have remained elevated.

Four of six patients who were exposed to fluoridated dialysate at our institution have undergone successful renal transplantation and have been free of skeletal complaints for

as long as 7 years, although three of the four had suffered fractures before and one immediately after transplantation.

Discussion

A number of studies have supported the conclusion that exposure to fluoridated dialysate increases the risk of symptomatic osteomalacia. Posen and co-workers (1971) noted an increased incidence of bone disease in the city of Ottawa, where fluoridated water was used to prepare the dialysate; and Cordy et al. (1974) reported a similar experience when patients who underwent dialysis at home used fluoridated water. The incidences of bone pain and fractures in Montreal (Cordy et al., 1974) were lower than those in our experience (Jowsey et al., 1972) and those reported in Ottawa (Posen, Marier, and Jaworski, 1971). Biopsy specimens from the iliac crest of four patients in Montreal who had the highest ratios of fluoride to calcium in bone were studied by Lough et al. (1975), using phase contract and electron microscopy. These biopsy specimens were compared with specimens from patients of similar age, sex, and duration of treatment who had been using fluoride-free dialysate. The studies differed in not having any adolescents and in dialysis mainly being done in a center rather than at home. In the nonfluoridated group, the findings were those of hyperparathyroid bone disease. On light microscopy, an increase was noted in the proportion of bone covered by osteoid in the fluoridated group. Cortical, cancellous, and periosteal bone showed abnormal mosaic patterns and staining characteristics. The number of osteoblasts was increased, and the canaliculi were in disarray. Electron microscopy confirmed an increase in osteoblasts and showed that their cytoplasmic processes were tangled and disarrayed. Collagen fibers were of normal diameter and periodicity but were loosely and irregularly aligned in bundles compared to the nonfluoridated group. Similar findings have been reported in cattle and dogs exposed to high fluoride intake--for example, osteoblastic cytoplasmic processes that produce collagen develop a haphazard, rootlike appearance, and the collagen that is produced is excessive in amount and lacks orderly orientation (Johnson, 1965).

Consistent with the thesis that fluoride contributes to osteomalacia is the report of Posen and co-workers (1972), who compared the incidence of osteodystrophy in patients dialyzed either with deionized water or with fluoridated tap water. Deionization was associated not only with less symptomatic osteomalacia but also with healing of prior osteomalacia. Because other elements as well as fluoride were removed by deionization, the authors suggested that

fluoride may contribute to the development of osteomalacia, but they could not exclude other factors.

In a study of the ionic composition of bone from uremic patients, Parsons and co-workers (1971) demonstrated uneven distribution of fluoride throughout the skeleton and concluded that the higher concentration of fluoride in certain areas was responsible for the increased osteoid in those locations. Siddiqui et al. (1970) reported that serum fluoride concentrations increased with time on dialysis and found a significant correlation between the severity of bone disease and the concentration of serum fluoride. Bone biopsy specimens from 17 patients revealed that the highest fluoride concentrations were present in those with severe osteomalacia. Kim and co-workers (1970) demonstrated a high content of fluoride in cortical bone of patients with renal disease whether or not they were treated with hemodialysis. The ratios of fluoride to calcium, however, were highest in the patients using fluoridated dialysate.

However, other studies have cast doubt on the hypothesis that the use of fluoridated dialysate causes more osteomalacia. Siddiqui and co-workers (1971) compared bone disease in patients from two cities in England: in patients from Birmingham, symptomatic osteodystrophy is uncommon and usually associated with osteitis fibrosa, while in patients from Newcastle, osteodystrophy is common and associated with multiple fractures but without roentgenographic evidence of osteitis fibrosa. Incrimination of fluoride in tap water as a cause of severe bone disease was not possible because both centers used fluoridated dialysate. Bone biopsy specimens were not examined in this study. Speculation as to the presence of some other toxic solute, as yet unidentified, was the best available explanation for the difference in attack rates of bone disease between the two cities. Oreopoulos and co-workers (1974) did a prospective double-blind study using deionized water to prepare the dialysate. In one group of patients, sodium chloride was added, while in the other, sodium fluoride was added to provide fluoride concentrations of 1 ppm in the final dialysate. Bone biopsy specimens obtained before treatment and after a year failed to show significant differences in the two groups except for increased sclerosis in the fluoride group. They concluded that dialysate fluoride is not the primary cause of progressive osteomalacia, at least during the first 2 years of dialysis.

Conflicting reports regarding the effects of fluoride in patients dialyzed using untreated tap water containing a high concentration of fluoride for preparation of the dialysate may be explained in a number of ways. Distinctive

roentgenographic changes associated with fluorosis may not be seen even after prolonged exposure, perhaps because renal failure alters the capacity of the dialyzed patient to respond by increasing bone production. Clinical manifestations of bone disease such as arthralgia, bone pain, and pathologic fractures depend on many variables other than fluoride. Therefore, the presence or absence of symptoms, fractures, or roentgenographic changes also is not a reliable index of a fluoride effect. In most instances, the only indications of the positive role of fluoride are an elevation of fluoride in blood and bone and the histologic changes demonstrated on bone biopsy. The significance of an elevation of serum fluoride alone may be ambiguous because increased bone resorption as a result of uncontrolled hyperparathyroidism also may lead to an elevation of serum fluoride. However, failure of the double-blind study to show a statistically significant increase in osteomalacia does not rule out some effect of fluoride. A small but not statistically significant difference in the expected direction was noted after a longer time (Oreopoulos, 1977). The control patients in the Oreopoulos study did not provide a clear contrast with the experimental group. Two of nine patients in the low fluoride group had long predialysis and prestudy exposure to fluoride. As a consequence, serum and bone fluoride concentrations of the two groups overlapped considerably. Also, the serum and bone fluoride concentrations they reported are lower than those noted in the Mayo Clinic (Jowsey et al., 1972) and the Montreal (Cordy et al., 1974) studies. The limitations of Oreopoulos' study may explain the failure to obtain a clear difference between the groups studied.

Concluding Remarks

The available evidence suggests that some patients with long-term renal failure are being affected by drinking water with as little as 2 ppm fluoride. All of the patients showed increased bone density, and two showed calcification of interosseous ligaments which is thought to be diagnostic of skeletal fluorosis (Stevenson and Wilson, 1957). The average concentration of fluoride in bone of 4.4 moles of fluoride per 100 moles of calcium is equivalent to 9,000 ppm of fluoride on an ash weight basis and is in the middle range of the values that have been reported for advanced fluorosis (Hodge and Smith, 1965; Jolly, Singh, and Mathur, 1969). The excessive osteoid formation seen in these patients is probably accentuated by fluoride.

With regard to the patients exposed to fluoridated dialysate, the presumption should probably be that fluoride has a definite but minor role in the development of osteomalacia.

The meaning of these findings for community fluoridation will depend on whether or not further work will clearly show adverse effects in patients with renal failure drinking water with a concentration of 1 ppm of fluoride and whether these effects can be easily avoided. The finding of adverse effects in patients drinking water with 2 ppm of fluoride suggests that a few similar cases may be found in patients imbibing 1 ppm, especially if large volumes are consumed, or in heavy tea drinkers and if fluoride is indeed a cause.

It would seem prudent, therefore, to monitor the fluoride intake of patients with renal failure living in high fluoride areas. The serum concentration may indicate whether the patient should be advised to drink low fluoride water and will provide a check regarding compliance. Tentatively, a shift to low fluoride water should be made before the serum fluoride concentration reaches 5 μM, since evidence of fluorosis has been reported when the average serum concentrations of fluoride are 8 μM (Leone et al., 1955; Singla, Garg, and Jolly, 1976).

In patients maintained by dialysis for long periods, fluoride-free dialysate should be used. There is insufficient evidence at this point to recommend the use of fluoride-free drinking water for all patients with renal disease.

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