Skeletal Scintigraphic Changes in Osteoporosis Treated with Sodium Fluoride: Concise Communication

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An appendicular skeletal response to sodium fluoride (NaF) was detected by total skeletal scintigrams. Twelve postmenopausal osteoporotic women were treated with NaF (88 mg/day) and calcium (1500 mg/day). Total skeletal scintigrams were obtained before and during treatment. Within 4 to 21 mo (mean: 8.3), all 12 patients showed new areas of increased uptake corresponding to metaphyseal regions and short bones of the appendicular skeleton. The number of peripheral bones involved in each subject ranged from four to 12. The most frequently involved sites (11 of 12 patients) were the right distal femur and proximal tibia. Nine patients showed an increase in serum alkaline phosphatase activity, which was attributed to an increase in the skeletal isoenzyme. Seven of 12 patients developed bone pain in one or more of the regions of increased uptake. This study establishes that the skeletal scintigram is a sensitive index of the peripheral skeletal response to NaF.


Recent evidence indicates that sodium fluoride is the single most effective agent in the treatment of spinal osteoporosis. NaF therapy has been shown to increase axial bone volume in the osteoporotic skeleton, as evidenced by increased spinal radiographic density, decreased vertebral fracture frequency, and decreased back pain (1–5). In the treatment of osteoporosis, NaF is the only available agent that unambiguously stimulates bone formation (2,6–8), although the mechanism of its action is not known. It is this osteogenic action that results in increased bone volume (2,9). In contrast to these positive actions of NaF on the axial skeleton, previous studies with osteoporotics have not demonstrated an effect of NaF on appendicular bone (1,2,10,11). Because there is need for an agent that acts on both the axial and appendicular skeleton, and because NaF has such a potent action on the axial skeleton, we decided to re-evaluate whether NaF acts on the appendicular skeleton. The rationale for utilizing skeletal scintigrams is that the amount of uptake of the bone-seeking tracer in a given skeletal site is largely determined by the regional rate of bone formation, and the action of NaF on the skeleton is to increase the bone formation rate.

PATIENTS AND METHODS

Twelve ambulatory white females, aged 57 to 77 yr (mean 66 yr), were studied. All had axial osteoporosis demonstrated by either one or more atraumatic vertebral compression fractures on spinal radiographs and/or a low spinal bone density on quantitative computerized tomography (12,13). Ten patients had primary osteoporosis and two had osteoporosis associated with malabsorption syndrome.

All patients were treated with NaF and calcium. They received 88 mg of NaF per day in divided doses, except for one patient who received 176 mg NaF per day. Dietary calcium was supplemented with calcium carbonate to provide a total intake of 1500 mg per day. Five of the 12 patients were also receiving an estrogen. Four of these
patients had started on their estrogen therapy before the start of this study. One estrogen-treated patient also received stanozolol, 6 mg/day, and another received vitamin D, 50,000 units daily.

Bone scintigrams were obtained with a total body scanner before NaF therapy followed by a repeat study 4 to 16 mo (mean 7.8) after therapy had begun. Six months later a subsequent bone scintigram was obtained in three patients. The bone scintigrams included anterior and posterior total-body views, obtained 2 to 2.5 hr after the administration of ~20 mCi of Tc-99m methylene diphosphonate. For each scintigram the scanner was set according to the average activity in the sternum and the spine. All scans were evaluated by three members of the nuclear medicine staff for regions of increased uptake.

Serum alkaline phosphatase activity (normal 11–38 units/l), and the skeletal isoenzyme component of that total (normal values have yet to be established), were measured (/4) at the time of each scintigram.

All subjects were interviewed at 3-mo intervals throughout treatment to evaluate pain. They were questioned regarding the onset, duration, location, and severity of symptoms.

RESULTS

All 12 pretherapy bone scintigrams were abnormal. Increased uptake was noted in: (a) the spine (n=11), (b) multiple regions in the ribs (n=3), (c) one shoulder (n=2), (d) the right great toe (n=1), and (e) both knees (n=1). In all of these studies the areas of increased uptake were consistent with either degenerative joint disease or fractures.

FIG. 1. Pretherapy image (left): Focal increased activity in midthoracic spine and L3 due to compression fractures. Slight asymmetry of hips, right being greater. First posttherapy study (4 mo on NaF, center): Marked diffuse increased activity in spine, right knee, and foot regions. Less marked in left knee, ankle-foot, and shoulders. Second posttherapy study (11 mo on NaF, right). Further increase in intensity and size of active regions, becoming more symmetrical, and mild increase in diaphyses of right femur and tibia.
All initial images, obtained after therapy was begun, showed new areas of increased uptake. In 11, these new sites in the peripheral skeleton corresponded to the distribution of trabecular bone—metaphyses of the long bones, and short bones such as the tarsal and carpal bones (Figs. 1 and 2). In two of these 11 images there was also increased uptake in the diaphyses of the femur and tibia. In two of these 11 patients the second posttherapy studies revealed further involvement in both the area and the number of regions affected (Fig. 1, right).

In the twelfth patient the posttherapy bone image was characterized by a generalized increased uptake in the spine as well as specifically increased uptake in the sacroiliac joints, without changes in the appendicular skeleton. The second posttherapy study, however, showed markedly increased activity in the distal femoral metaphyses.

In all patients, two or more sites of the appendicular skeleton were affected (Table 1), most frequently in the lower extremities (Table 2). The distribution was usually bilateral. However, when the increased uptake was not symmetrical, the sites most frequently affected were on the right side.

The increased activity resulting from NaF therapy extended farther into the metaphyseal region (Fig. 1) than is usually noted in degenerative joint disease (Fig. 2, left). In the posttherapy bone images there was a photopenic line in the knee corresponding to the joint space (Fig. 1), which is generally obliterated in degenerative joint disease (Fig. 2, left).

At the time of the first posttherapy study, ten patients (83%) did not complain of pain in any of the areas of increased activity. Two patients (17%) complained of moderate pain in at least one of the affected regions. Five patients developed pain in an affected region within 2 to 6 mo after the first posttherapy bone studies. Two patients had normal conventional radiographs at painful sites. The symptoms did not respond to treatment with mild analgesics or nonsteroidal antiinflammatory agents. Temporary arrest of NaF therapy, however, reduced pain immediately, with complete relief from pain within 2 to 3 wk in all affected patients.

The serum total alkaline phosphatase activity was significantly increased (p < 0.02) from 29.9 ± 9.5 units/l at the time of the pretherapy studies to 65.9 ± 36.8 at the time of the posttherapy images. This increase was attended by a significant increase (p < 0.02) in the serum skeletal alkaline phosphatase isoenzyme activity from 18.6 ± 10.4 units/l at the time of the pretherapy images to 42.3 ± 23.6 at the time of the first posttherapy studies. The change in serum total alkaline phosphatase activity correlated with the change in the serum skeletal alkaline phosphatase isoenzyme activity (r = 0.86, p < 0.001). Serum skeletal alkaline phosphatase isoenzyme activity was unchanged in only three patients. Two of these showed minimal changes on bone scintigrams (e.g., increased uptake only in the spine or in the distal right foot and left shoulder). One patient, however, had six or more regions of increased uptake without an increase in total or skeletal alkaline phosphatase isoenzyme activity.

**DISCUSSION**

The results of this study suggest that NaF therapy in osteoporosis effects an increased bone formation in the appendicular skeleton as well as in the axial. In all patients the total skeletal scintigrams after NaF therapy showed increased uptake in the appendicular bones. This finding was unexpected because previous studies, (primarily using single-photon absorptiometry of the distal radius) had reported no affect of NaF on the appendicular skeleton (1,2,10,11). Our results suggest that skeletal scintigrams may provide a more sensitive method for identifying the action of NaF on peripheral
bone. By this means we observed a response to NaF in the regions of the appendicular skeleton that are rich in trabecular bone. Although we believe that the increased uptake of Tc-99m methylene diphosphonate reflected increased bone formation, we cannot exclude the possibility that augmented blood flow contributed to the increased uptake. Augmented blood flow did not entirely account for the observed changes, however, because the maximum increase in uptake, per unit volume, that can be attributed to augmented circulation alone is only twice that seen with normal circulation (15), and the increases we observed were often much greater than twofold.

In addition to this evidence for an affect of NaF on the peripheral skeleton, our data suggest an earlier response to NaF in areas under greater mechanical stress (6). All our patients exhibited sites of increased activity (relative to vertebrae and sternum) predominately in the weight-bearing bones of the appendicular skeleton. In one patient, whereas the first posttherapy image showed increased uptake only in the axial skeleton (i.e., spine and sacro-iliac joints), the second study showed increased activity in the peripheral skeleton.

We were surprised to observe such an early response to NaF in all patients. We observed new areas of increased uptake in every patient. In the majority of cases this response to NaF was detected within 6 mo of treatment. This contrasts greatly with previous studies (1–3) reporting only 40–60% of osteoporotics who (as judged by spinal radiographs and/or bone histomorphometry) responded to NaF within 2 to 6 yr. Our own previous study (16), using increases in serum alkaline phosphatase activity as an index of the skeletal response to NaF, demonstrated that 80% of osteoporotics responded to NaF within 2 yr of treatment and that half of those patients had responded within 7 mo. Studies of endemic or industrial fluorosis (17–21) report at least 4 yr of exposure before skeletal changes could be detected by radiographs. The National Institute for Occupational Safety and Health has suggested that workers exposed to fluoride be screened by x-ray before employment and every 6 yr thereafter (22). Because of the small number of patients in the current study, we are limited in the conclusions we can make regarding the incidence and the onset of the response to NaF. We can conclude, however, that total skeletal scintigrams, which measure bone activity rather than bone volume—and also measure local rather than total skeletal response—afford a sensitive method for future determinations of the incidence and onset of the skeletal response to NaF.

Note also that this new evidence of a response to NaF in the metaphyses of the appendicular skeleton may provide an explanation for the complaints of rheumatic pain that have been associated with NaF therapy. Riggs et al. reported a 42% incidence of rheumatic reactions resembling either synovitis, primarily of the ankle or knee, or painful plantar fascial syndrome of one or both feet in osteoporotics treated with 44 mg NaF per day (1). Similar rheumatic symptoms, in an even greater percentage of patients, have been observed by others treating osteoporotics with NaF (11,23), as well as in patients with fluorosis due to endemic conditions and industrial contamination (17–19,21,24). There was a similar incidence (58%) of arthralgia in the current study. In all patients the complaints of periarticular pain corresponded to regions of increased uptake on skeletal scintigrams. In the majority of cases (82%), however, the findings on bone scintigrams preceded the associated pain. Note also that all patients had asymptomatic regions of increased uptake. This rheumatic pain in response to fluoride has been attributed to new or aggravated degenerative joint disease (23,25). The features of the regions of increased uptake that we observed in our patients were not consistent with degenerative joint disease. However, one of the side effects of NaF toxicity is painful periostitis (24). Thus it is possible that in NaF treated patients the pain in the region of joints may, in some if not most instances, represent metaphyseal periostitis rather than an aggravation of degenerative joint disease.

Since fluoride is being used with increasing frequency in the treatment of osteoporosis, the results of this study should alert physicians to the possibility that unusual or unexpected areas of increased activity in bone scintigrams of osteoporotics, especially in the appendicular skeleton, may be due to NaF treatment.

In conclusion, our data indicate that the skeletal response to NaF in osteoporotic subjects is not limited to the axial skeleton, and suggest that bone scanning may be a useful tool for assessing the peripheral skeletal response to NaF therapy. The method may also be useful for evaluating industrial and endemic exposure to fluoride.

REFERENCES


