Sustained-Release Sodium Fluoride in the Treatment of the Elderly With Established Osteoporosis

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Background: We ascertained the safety and efficacy of fluoride in augmenting spinal bone mass and reducing spinal fractures in older women with established osteoporosis. We compared a combination of sustained-release sodium fluoride, calcium citrate, and cholecalciferol (SR-NaF group) with calcium and cholecalciferol alone (control group).

Methods: Eighty-five ambulatory women aged 65 years or older with 1 or more nontraumatic vertebral compression fractures were enrolled in a 42-month randomized, double-blind, placebo-controlled trial. Primary outcome measures were vertebral fracture rate, bone mass, and safety.

Results: The vertebral fracture rate determined by means of computer assistance in the SR-NaF group was significantly lower than that in the control group (relative risk [RR], 0.32; 95% confidence interval [CI], 0.14-0.73; P = .007). Results of visual adjudicated inspection also confirmed a significant reduction in fracture rate (RR, 0.40; 95% CI, 0.17-0.95; P = .04). Bone mineral density in L2 through L4 increased significantly from baseline in the SR-NaF group by 5.4% (95% CI, 2.7%-8.2%; P < .001), and by 3.2% in the control group (95% CI, 0.8%-5.6%; P = .01). The between-group differences in bone mineral density were not significant. The femoral neck and total hip bone mineral density remained stable in the SR-NaF group and was not significantly different from that of the control group. There were no significant differences in adverse effects between groups.

Conclusion: The SR-NaF group significantly decreased the risk for vertebral fractures and increased spinal bone mass without reducing bone mass at the femoral neck and total hip.

Arch Intern Med. 2001;161:2325-2333

OSTEOPOROSIS is a common and morbid problem whose impact on public health will increase as the population ages.

The pathophysiology of osteoporosis in the late postmenopausal period is believed to be related to senescent changes in osteoblastic function resulting in a decline in bone formation. In addition, bone turnover may increase with aging. The latter appears in part because of impaired calcium absorption resulting in secondary hyperparathyroidism. In this way, calcium homeostasis is maintained at the expense of bone mass. The adequate provision of calcium and vitamin D can suppress parathyroid function and reduce bone turnover.

Calcium and cholecalciferol (vitamin D) supplementation in older patients has been shown to decrease risk for fracture. During the past decade, new pharmacological interventions have become available to treat osteoporosis. These agents are directed primarily toward the inhibition of osteoclastic activity, thereby reducing bone resorption and turnover.

At present, there are no approved anabolic or bone-forming agents available for treating osteoporosis. Such therapies influence bone mass through the stimulation of osteoblastic activity, resulting in increased bone mass. Sodium fluoride is known to stimulate bone formation. When administered in low doses, bone mass is increased and risk for vertebral fractures is reduced in patients with osteoporosis. However, uncertainty remains about the efficacy and safety of sodium fluoride. In studies of patients with osteoporosis treated with continuous and/or high-dose sodium fluoride, the risk for vertebral fractures was unchanged compared with that of controls, despite increases in spinal bone mass in the sodium fluoride–treated group. In addition, increased numbers of nonvertebral fractures in sodium fluoride–treated patients raised concern about impaired bone quality and reduced bone strength. Moreover, serious adverse effects have
SUBJECTS AND METHODS

SUBJECTS

Women aged 65 years or older with at least 1 nontraumatic vertebral compression fracture were recruited by means of newspaper advertisements for the study. The protocol was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas. Patient recruitment, study design, and conduct of the trial were performed by one of us (C.D.R.), with nursing, dietary assessment, basic laboratory, and statistical support by staff of the General Clinical Research Center at the University of Texas Southwestern Medical Center. Additional support included special laboratory analysis and fracture determination as described herein.29

Prospective subjects underwent initial screening and evaluation for the purpose of verifying the presence of established osteoporosis and to exclude secondary causes of osteoporosis. A thorough medical history was obtained. Subjects were excluded from participation if they had a history of active peptic ulcer disease, nephrolithiasis, primary hyperparathyroidism, inflammatory bowel disease, or long-term use of oral steroids or phenytoin sodium. Because of historical concern regarding the possibility of increased risk for hip fractures with sodium fluoride therapy, patients with a history of hip fracture were excluded. Patients were also excluded if they had taken a bone active agent within the past year (eg, calcitonin, bisphosphonate) or ever (sodium fluoride). Routine screening laboratory studies included a complete blood cell count; measurement of electrolyte, glucose, creatinine, liver enzyme, thyrotropin, and parathyroid hormone (PTH) levels; serum protein electrophoresis; and routine urinalysis. Dietary calcium intake was estimated by a registered dietitian using a food frequency questionnaire.

The protocol specifically attempted to recruit a cohort of women representative of a typical outpatient population of older women with osteoporosis. Therefore, patients commonly had multiple medical problems and complaints. For example, patients with a history of GI tract complaints, musculoskeletal complaints, concurrent use of aspirin or anti-inflammatory medications, or use of agents to treat GI tract disorders were included. Patients with musculoskeletal complaints were carefully asked the location, severity, and character of complaints to monitor for potentially new or worsening symptoms during the study. In addition, because estrogen is commonly used and recommended for a variety of reasons in a typical population of postmenopausal women, current estrogen use (stable dose for at least the past year) was allowed, but patients were stratified to ensure equal distribution between groups.

A baseline lateral thoracic and lumbar x-ray film was obtained to confirm the presence of at least 1 vertebral compression fracture from T4 through L5, defined as at least a 20% reduction in anterior, middle, or posterior vertebral height in the absence of significant trauma. There was no bone mineral density (BMD) requirement for study entry.

RANDOMIZATION AND TREATMENT SCHEME

Once patients met entry criteria, they were randomly assigned to receive sustained-release sodium fluoride, 25 mg (Neosent; Mission Pharmacal Company, San Antonio, Tex) (SR-NaF group), or a placebo of identical appearance taken in the morning and at bedtime (control group). Both groups received calcium with cholecalciferol (Citracal with Vitamin D; Mission Pharmacal Company) in 3 divided doses (total dose, 945 mg of elemental calcium citrate and 600 IU of cholecalciferol daily). To ensure a balanced distribution of prognostic variables between groups, patients were dynamically randomized to the SR-NaF or control group with the use of biased-coin minimization30 to stratify on the basis of age, baseline L2 through L4 BMD, prevalent fractures, and estrogen use. The clinical investigators, General Clinical Research Center personnel with patient contact, and patients were unaware of subject randomization and assignment throughout the study. Independent research personnel performed the randomization and had no other study participation. Treatment was given for 3 cycles, each cycle consisting of a 12-month administration of sustained-release sodium fluoride or placebo followed by a 2-month period free of study medication. The intermittent format of administration was devised to help ensure adequate mineralization of newly formed bone and to avoid the accumulation of toxic fluoride levels in the bone.31 Calcium and cholecalciferol were given continuously for 42 months.

BIOCHEMICAL MEASUREMENTS

At baseline and 3, 6, 9, 12, and 14 months of each cycle, a multisystem screening of serum (SMA-20; Smith-Kline Laboratory, Dallas, Tex); complete blood cell count; reticulocyte count; levels of serum fluoride (ion-specific electrode), 24-hour urinary calcium (using atomic-absorption spectrophotometry), and 24-hour urinary N-telopeptide (using an enzyme-linked immunosorbent assay; Ostex International, Inc, Seattle, Wash); and presence of occult blood in feces were measured. In addition, at baseline and 6, 12, and 14 months of each cycle, we tested for levels of serum PTH (whole-molecule immunoradiometric assay using a kit from Nichols Institute, San Juan Capistrano, Calif), serum bone-specific alkaline phosphatase (BSAP) (Metra Biosystems, Mountain View, Calif), and serum osteocalcin (using an immunoradiometric assay; Immutopics, Inc, San Clemente, Calif). Levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were obtained to confirm the presence of at least 1 vertebral compression fracture from T4 through L5, defined as at least a 20% reduction in anterior, middle, or posterior vertebral height in the absence of significant trauma. There was no bone mineral density (BMD) requirement for study entry.

Because age-related bone loss is due to decreased bone formation and altered calcium metabolism, we postulated that an appropriate therapeutic intervention for treating age-related osteoporosis would incorporate an anabolic agent to stimulate osteoblastic activity and adequate calcium and cholecalciferol to blunt secondary hyperparathyroidism and to reduce mobilization of calcium from the skeleton.
determined at baseline and every 12 months as previously described.12,34

BONE MASS MEASUREMENTS

Bone mineral density of the L2 through L4 lumbar spine, femoral neck, and total hip were measured by means of dual-energy x-ray absorptiometry using a scanner (Hologic QDR-2000; Hologic, Waltham, Mass) at baseline and 6 and 12 months of each cycle. The coefficient of variation, based on manufacturer-supplied information for measurement of L2 through L4 and hip BMD, was 1%.

FRACTURE DETERMINATION

Lateral spine films were obtained annually to detect new or recurrent fractures. Incident fractures occurring at all cycles were determined by means of computer-assisted analysis in Dallas (quantitative morphometry [QM-Dallas]). Fracture quantitation by means of the QM-Dallas technique used a digitizing board and computer program to measure vertebral heights and area.35 Six landmarks were placed to outline the anterior, middle, and posterior height of T4 through L5 from lateral thoracic and lumbar films obtained at the end of each 12-month treatment cycle. The analysis was performed by a single trained technician with no patient contact and who was unaware of treatment assignment. The intraincisor precision was 1.5%. A computer program calculated the change in each vertebral height and area, after correcting for magnification error between cycles. A reduction in height of more than 20% and in area of at least 10% from baseline defined a new fracture.36

In addition, the first and final films (pretreatment and last cycle) were examined by using the following methods (72 subjects). Quantitative morphometry was also determined by external analysis (performed by H.K.G. and J.L. [San Francisco (SM) group]) using their own software, but with the same fracture criteria as QM in Dallas. Radiographs were visually inspected for qualitative determination of incident fractures independently by an external expert (D.S.R.) and an internal expert (Khashayar Sakhaee, MD). No specific definition of a fracture was given to the reviewers. The reviewers were asked to assess baseline and final radiographs to identify vertebral fractures that had newly appeared or worsened from baseline, and that they believed to be permanent deformations. All experts were unaware of group assignment and measurements from the QM-Dallas data.

A planned fracture analysis was used to evaluate “discordant” vertebrae findings between results of the Dallas group and QM-SF group. For first and last films, a consensus reading from Dallas was defined by an agreement of 2 of 3 analyses (QM-Dallas and both independent visual reviews). The results of this consensus reading from Dallas were compared with the QM-SF findings, and vertebrae with differing fracture status were identified from each patient. The discordant vertebrae findings so identified were examined visually by the SF investigators. The results of their joint visual reading replaced the discordant fracture status of vertebrae to yield the adjudicated result of the Dallas and SF groups.

There was good to excellent agreement between the QM-Dallas and other techniques to assess incident fractures (Sakhaee visual, κ = 0.83; D.S.R. visual, κ = 0.74; QM-SF unadjusted, κ = 0.73; SF adjudicated, κ = 0.84).

SAFETY EVALUATION

Subjects underwent evaluation for adverse effects every 3 months. Subjects were specifically queried regarding the development of any new or worsening GI tract or musculoskeletal symptoms using a questionnaire. Subjects were questioned about the presence of lower extremity discomfort, including shin pain. Stool specimens were obtained every 3 months to test for fecal occult blood.

Research nurses performed pill counts of code pills (sodium fluoride or placebo) during each follow-up visit. Calcium tablets were not counted.

STATISTICAL ANALYSIS

Baseline characteristics were summarized using descriptive statistics. Because some patients had multiple vertebral fractures, differences in vertebral fracture rates between the control and SR-NaF groups were assessed using correlated binary regression models with generalized estimating equations.37 The correlated binary regression method was applied to the incident fracture data from pretreatment to the last cycle obtained by means of QM-Dallas, adjudicated-Dallas, and SF methods. Covariates such as estrogen use and initial BMD were assessed in these models. In addition, incident fracture data at all cycles obtained by means of the QM-Dallas method were analyzed using Cox proportional hazards models for analysis of multiple failure times with the marginal approach of Wei et al.38 and Lin.39 The number needed to treat was calculated as the reciprocal of the absolute risk reduction.40

Results of bone densitometry were assessed using repeated-measures analysis of variance and change from baseline with the use of paired t tests. Biochemical measurements were assessed using repeated-measures analysis of variance. Adverse events were compared between groups using the Fisher exact test.

Statistical analysis was performed at the General Clinical Research Center using commercially available software (SAS version 8.0; SAS Institute, Cary, NC). We used SAS macros written by Terry Therneau, PhD, of Mayo Clinic, Rochester, Minn, for Cox regression analysis of multivariate failure times.

To study the effect of this strategy, we conducted a randomized, double-blind, controlled trial comparing the safety and efficacy of an anabolic agent in the form of sustained-released sodium fluoride combined with calcium citrate and cholecalciferol with those of calcium and cholecalciferol alone in elderly women with established age-related osteoporosis. We herein report the results of this study.

RESULTS

BASELINE PRESENTATION

The mean age of study participants was 73 years, with approximately 26 years since menopause. Baseline characteristics were similar in the SR-NaF and control groups.
Eighty-five subjects were randomized, of whom 13 withdrew in the first 6 months before completing the first cycle. None of these early withdrawals were due to study-related adverse events. Nine of the 13 early withdrawals failed to return for the first follow-up visit at 3 months. Two patients (1 from each group) had hip fractures within a month of beginning treatment. Lack of interest and transportation problems were the most common reason for the early withdrawals. Seventy-two subjects (85%) completed at least 1 cycle of therapy (14 months). Sixty-five subjects (76%) completed all 3 cycles (42 months). The mean (±SD) duration of treatment was 2.9±0.4 cycles for the SR-NaF and control groups.

**Subjects and Methods** section.

Treatment groups are described in the “Subjects” subsection of the “Subjects and Methods” section. BMI, body mass index.

The analysis of spinal fracture data during the 3 treatment cycles by means of correlated binary regression showed a 68% rate reduction of new or recurrent fracture in the SR-NaF group compared with the control group, when fractures were quantitated by means of the QM-Dallas technique (relative risk [RR], 0.32; 95% confidence interval [CI], 0.14-0.73; P = .007). A 60% reduction in the fracture rate in the SR-NaF group was seen when fractures were detected by means of the adjudicated Dallas and SF techniques (RR, 0.40; 95% CI, 0.17-0.95; P = .04). When an analysis was performed for the number needed to treat, 8 patients needed to be treated to prevent 1 vertebral fracture by means of the QM-Dallas technique, and 9 patients were needed by means of the adjudicated-Dallas and -SF techniques.

For spinal fractures detected by means of QM-Dallas technique from all cycles of treatment, the multivariate Cox model showed a significantly lower relapse rate in the SR-NaF group compared with that in the control group (RR, 0.31; 95% CI, 0.13-0.73; P = .007).

Estrogen use was not a significant covariate (RR, 0.97; P = .96) for fracture in assessing fracture risk. In addition, there were no differences between estrogen users and nonusers in baseline demographic or clinical characteristics.

There were no differences in the number of nonvertebral fractures between groups. One hip fracture occurred in each group (in addition to 2 early withdrawals). Seven nonvertebral fractures occurred in each group. These included 1 wrist, 1 metacarpal, 1 humeral, 1 femur, and 3 toe fractures in the SR-NaF group, and 2 patellar, 3 rib, 1 wrist, and 1 toe fracture in the control group.

### BMD DATA

After 3 treatment cycles, L2 through L4 BMD increased by 5.4% (95% CI, 2.7%-8.2%; P < .001) in the SR-NaF group and by 3.2% (95% CI, 0.8%-5.6%; P = .01) in the control group. There were no significant differences between groups (95% CI, −1.2% to 5.8%). In both groups, BMD was maintained at the femoral neck and total hip.

### FRACTURE DATA

The analysis of spinal fracture data during the 3 treatment cycles by means of correlated binary regression showed a 68% rate reduction of new or recurrent fracture in the SR-NaF group compared with the control group, when fractures were quantitated by means of the QM-Dallas technique (relative risk [RR], 0.32; 95% confidence interval [CI], 0.14-0.73; P = .007). A 60% reduction in the fracture rate in the SR-NaF group was seen when fractures were detected by means of the adjudicated Dallas and SF techniques (RR, 0.40; 95% CI, 0.17-0.95; P = .04). When an analysis was performed for the number needed to treat, 8 patients needed to be treated to prevent 1 vertebral fracture by means of the QM-Dallas technique, and 9 patients needed to be treated to prevent 1 vertebral fracture by means of the adjudicated-Dallas and -SF techniques.

### Table 2. Vertebral Fractures*

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>SR-NaF Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration, mean ± SD</strong></td>
<td>2.9 ± 0.4</td>
<td>2.9 ± 0.4</td>
</tr>
<tr>
<td><strong>No. (%) of patients with fractures</strong></td>
<td>8 (24)</td>
<td>14 (37)</td>
</tr>
<tr>
<td><strong>No. of fractures</strong></td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td><strong>Total No. of cycles</strong></td>
<td>97</td>
<td>110</td>
</tr>
<tr>
<td><strong>Fracture, No. per cycle</strong></td>
<td>0.10</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Relative risk, SR-NaF/control groups (95% CI)</strong></td>
<td>0.32 (0.14-0.73; P = .007)</td>
<td>0.40 (0.17-0.95; P = .04)†</td>
</tr>
<tr>
<td><strong>No. needed to treat</strong></td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

*QM-Dallas evaluation was obtained at every cycle. Adjudicated Dallas and San Francisco evaluation used baseline and last films only. QM indicates quantitative morphometry; CI, confidence interval. Treatment groups are described in the “Subjects” and evaluations in the “Fracture Determination” subsections of the “Subjects and Methods” section.

†One final (cycle 3) x-ray film was not available for examination by the San Francisco group but was found to have 1 fracture by means of QM-Dallas evaluation. If this fracture is included in adjudicated Dallas and San Francisco analysis, the relative risk is 0.42 (95% CI, 0.18-0.98; P = .04; No. needed to treat, 13).

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Serum and urinary variables of bone metabolism for the 12-month visit of each cycle are reported in Table 3. Urinary N-telopeptide levels, reflecting bone resorption, declined in the control group and were maintained in the SR-NaF group. Urinary hydroxyproline levels followed a similar trend. Urinary calcium levels increased in both groups but to a lesser degree in the SR-NaF group. The SR-NaF group showed significant increases in markers of bone formation compared with the control group. The BSAP response was significantly higher in the SR-NaF group than in the control group ($P=.009$). Differences in BSAP response were not significant in samples measured at the end of the 2-month period free of study medication, but once sodium fluoride therapy was reinitiated, levels increased significantly in the SR-NaF group. Levels of serum osteocalcin during treatment were also significantly higher ($P=.01$) in the SR-NaF group compared with the control group (Figure 2).

Serum PTH levels tended to decline similarly in both groups, but this trend was significant in the SR-NaF group ($P=.045$) and was borderline ($P=.12$) in the control group. Serum levels of 25-dihydroxyvitamin D increased significantly in both groups compared with baseline ($P<.01$) and were not different between groups. Levels of 1,25-dihydroxyvitamin D tended to fall in both groups. Serum calcium and phosphorus levels remained stable and without significant differences between groups during the 3-year study.

**SAFETY**

There were no differences observed in GI tract and musculoskeletal adverse effects between the SR-NaF and control groups. No subject withdrew from the study because of adverse effects.

Occult blood in stool was identified in 7 patients: 4 in the SR-NaF group and 3 in the control group. In the SR-NaF group, occult GI tract bleeding developed in 1 patient who was also receiving a nonsteroidal anti-inflammatory drug. Endoscopy disclosed peptic erosions. The nonsteroidal anti-inflammatory drug therapy was discontinued and histamine blockers were prescribed. Patient enrollment continued (blinding was maintained). Erosion healing was documented by subsequent endoscopy findings. The subject completed the study with no recurrence of occult GI tract blood loss. One patient receiving hormone replacement therapy was menstruating during a single follow-up, with subsequent negative findings for occult blood in stools, and 1 patient had positive findings during a hemorrhoidal flare. One patient dropped out after 2 months in the study because of bright red blood in the rectum (undocumented) and “too hectic a personal schedule to participate in the study.” In the control group, 1 patient was menstruating while receiving hormone replacement therapy, 1 patient experienced hemorrhoidal flare, and a gastric ulcer developed in 1 patient.

Adverse effects previously associated with higher doses of sodium fluoride therapy were absent. The prevalence of any history of musculoskeletal complaint in both groups was high. Complaints of at least 1 intermittent musculoskeletal problem of a chronic nature at enrollment were made by 95% (42/44) of the SR-NaF group and 98% (40/41) of the control group. Specifically, no symptoms developed suggestive of acute lower extremity pain syndromes. Although bone scans were available to assess for microfractures and/or to evaluate acute lower extremity pain, neither were indicated.

The number of adverse effects in the GI tract was similar between groups. At baseline, 70% of patients in the SR-NaF group and 51% in the control group had noted at least 1 chronic GI tract complaint. A new episode of transient dyspepsia was reported sometime during the 42-month trial in 14 subjects (32%) in the SR-NaF group and 14 (34%) in the control group.

Compliance, determined by pill count at each visit, found that patients in the SR-NaF group were compliant 73% of the time compared with 71% for the controls. Seven patients withdrew after completing 1 cycle: 4 were in the SR-NaF group and 3 in the control group. Causes of withdrawal were hip fracture in 1 patient in...
the SR-NaF group, gastric ulcer in 1 patient in the control group, emphysema and suspected lung cancer in a patient with a smoking history in the control group, death due to natural causes in 1 patient in the control group, use of other bone active agents or steroids in 2 patients in the SR-NaF group, and failure to return in 1 patient in the SR-NaF group. Another control group patient had a hip fracture at the end of the study but completed the study. One patient in each group had an esophageal ulcer, but both completed the study.

Our findings show that the combination therapy consisting of sustained-release sodium fluoride, calcium, and cholecalciferol in older women with established osteoporosis significantly reduced the risk for subsequent vertebral fractures compared with cholecalciferol and calcium therapy alone. The reduction in vertebral fracture rate and increased vertebral BMD occurred without reducing bone mass at the hip or increasing nonvertebral fractures. The redistribution of bone mass from other sites to the spine has been a commonly held concern regarding sodium fluoride therapy.26

Increases in biochemical markers of bone formation in the SR-NaF group suggest that the mechanism of fracture reduction was stimulation of bone remodeling and bone formation. These findings support achievement of reductions in vertebral fracture risk by combining a formation-stimulating and/or antiresorptive agent.41

Table 3. Serum and Urinary Biochemical Findings After Treatment With Placebo or Sustained-Release Sodium Fluoride

<table>
<thead>
<tr>
<th>Laboratory Values, Treatment Group</th>
<th>Baseline</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Comparison Between Treatment Groups, P Valuea</th>
<th>Comparison Within Treatment Groups, P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary N-telopeptide, nmol BCE/dd</td>
<td>Control</td>
<td>241 ± 190 (38)</td>
<td>171 ± 120 (38)</td>
<td>188 ± 99 (37)</td>
<td>185 ± 79 (34)</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>SR-NaF</td>
<td>230 ± 178 (34)</td>
<td>225 ± 165 (34)</td>
<td>272 ± 214 (33)</td>
<td>240 ± 155 (28)</td>
<td>.31</td>
</tr>
<tr>
<td>Median</td>
<td>Control</td>
<td>197</td>
<td>160</td>
<td>191</td>
<td>213</td>
<td>.78</td>
</tr>
<tr>
<td></td>
<td>SR-NaF</td>
<td>141 ± 78 (34)</td>
<td>209 ± 79 (38)</td>
<td>199 ± 86 (37)</td>
<td>208 ± 102 (34)</td>
<td>.07</td>
</tr>
</tbody>
</table>

Urinary hydroxyproline, mg/d:
|                                    | Control  | 14.3 ± 4.6 (38) | 13.8 ± 5.2 (38) | 12.6 ± 4.4 (37) | 11.8 ± 6.6 (34) | .78 |
|                                    | SR-NaF   | 16.2 ± 6.3 (34) | 15.2 ± 6.9 (34) | 15.8 ± 8.7 (33) | 13.3 ± 5.3 (32) | .43 |

Urinary calcium, mg/d:
|                                    | Control  | 141 ± 78 (34) | 209 ± 79 (38) | 199 ± 86 (37) | 208 ± 102 (34) | .07 |
|                                    | SR-NaF   | 131 ± 73 (34) | 181 ± 86 (34) | 182 ± 98 (33) | 181 ± 98 (29) | .07 |

Serum bone-specific alkaline phosphatase, U/L:
|                                    | Control  | 15.8 ± 6.4 (38) | 14.1 ± 4.8 (38) | 16.3 ± 5.8 (37) | 14.6 ± 6.4 (35) |
|                                    | SR-NaF   | 15.5 ± 6.9 (34) | 18.2 ± 9.3 (34) | 19.2 ± 9.7 (33) | 17.7 ± 8.2 (28) |

Serum osteocalcin, ng/mL:
|                                    | Control  | 6.4 ± 3.0 (36) | 5.1 ± 2.0 (38) | 5.2 ± 1.8 (37) | 4.6 ± 1.6 (34) | .009 |
|                                    | SR-NaF   | 6.5 ± 3.7 (31) | 6.7 ± 2.5 (34) | 6.5 ± 3.0 (33) | 6.7 ± 3.2 (28) | .002 |

Serum parathyroid hormone, pg/mL:
|                                    | Control  | 39.9 ± 14.4 (38) | 32.8 ± 11.3 (38) | 35.6 ± 12.2 (37) | 35.1 ± 14.5 (35) | .01 |
|                                    | SR-NaF   | 40.8 ± 13.9 (34) | 35.1 ± 11.4 (34) | 36.6 ± 12.1 (33) | 39.1 ± 11.1 (28) | .045 |

Serum 25-hydroxyvitamin D, ng/mL:
|                                    | Control  | 26.4 ± 11.3 (33) | 34.8 ± 7.9 (38) | 35.4 ± 7.9 (37) | 35.7 ± 7.9 (34) | .28 |
|                                    | SR-NaF   | 28.9 ± 15.4 (34) | 38.1 ± 14.8 (34) | 39.9 ± 9.8 (32) | 41.6 ± 14.9 (28) | .001 |

Serum 1,25-dihydroxyvitamin D, pg/mL:
|                                    | Control  | 35.1 ± 10.7 (38) | 30.4 ± 14.2 (38) | 26.7 ± 11.1 (37) | 24.0 ± 8.0 (34) | .48 |
|                                    | SR-NaF   | 34.2 ± 14.0 (34) | 32.7 ± 12.7 (34) | 30.2 ± 10.2 (32) | 28.5 ± 10.1 (28) | <.001 |

Serum 25-hydroxyvitamin D, pg/mL:
|                                    | Control  | 9.4 ± 0.4 (34) | 9.8 ± 0.4 (38) | 9.7 ± 0.5 (37) | 9.4 ± 0.4 (35) | .77 |
|                                    | SR-NaF   | 9.5 ± 0.4 (34) | 9.6 ± 0.4 (34) | 9.7 ± 0.4 (33) | 9.6 ± 0.4 (28) | .79 |

a Unless otherwise indicated, data are expressed as mean ± SD (number of subjects). Only 12-month visits of each cycle are summarized here. All visits were included in the models for analysis. Treatment groups are described in the “Subjects” subsection of the “Subjects and Methods” section. BCE indicates bone collagen equivalents; SR-NaF, sustained-release sodium fluoride.
b Indicates the interaction between treatment group and duration of study (month) from repeated-measures analysis of variance models and represents the difference in response between groups.
c Indicates the changes during the period of study within each treatment group from repeated-measures analysis of variance.
d Reference range, 45-803 nmol of BCE/d.
e Reference range, <40 mg/d.
f Reference range, <250 mg/d.
g Reference range, 14.2-42.7 U/L.
h Reference range, 2.4-10.0 ng/mL.
i Reference range, 10-65 pg/mL.
j Reference range, 8-42 pg/mL.
k Reference range, 18-52 pg/mL.
l To convert to millimoles per liter, multiply by 0.25.
m To convert to millimoles per liter, multiply by 0.25.

Our findings show that the combination therapy consisting of sustained-release sodium fluoride, calcium, and cholecalciferol in older women with established osteoporosis significantly reduced the risk for subsequent vertebral fractures compared with cholecalciferol and calcium therapy alone. The reduction in vertebral fracture rate and increased vertebral BMD occurred without reducing bone mass at the hip or increasing nonvertebral fractures. The redistribution of bone mass from other sites to the spine has been a commonly held concern regarding sodium fluoride therapy.26

Increases in biochemical markers of bone formation in the SR-NaF group suggest that the mechanism of fracture reduction was stimulation of bone remodeling and bone formation. These findings support achievement of reductions in vertebral fracture risk by combining a formation-stimulating and/or antiresorptive agent.41
Lumbar BMD increased significantly compared with baseline in both groups, but between-group differences were not significant. Furthermore, the increase in BMD was not as large as in a previously reported trial using sustained-release sodium fluoride. There may be multiple reasons for this finding. First, spinal BMD measurements are commonly difficult to assess in older patients because of degenerative spinal changes that present technical difficulties in assessing spinal BMD. A review of L2 through L4 spinal films found 14 subjects with severe scoliosis, aortic calcifications, severely collapsed vertebrae, or sclerotic degenerative arthritis. The clarity of individual radiographs at baseline was not used as a consideration for study entry. That is, a single vertebral compression was required for entry, but other qualitative radiographic aspects were not considered. Although this method has limitations for BMD and fracture analysis, the study was designed to enroll a typical ambulatory population of elderly patients. To exclude older patients because of degenerative spinal changes could have hindered this goal.

Second, the lack of a difference in BMD between groups may be related to the dose of calcium and calcitriol given to all subjects. Both groups received substantially higher doses of calcium and calcitriol than in most clinical studies of osteoporosis, including an earlier study by Pak et al using sustained-release sodium fluoride. Indeed, the doses used are consistent with recommendations made by the Institute of Medicine’s Food and Nutrition Board in 1997, which recommended 600 IU of calcitriol for persons older than 70 years, and the 1994 Consensus Development Panel for Optimal Calcium Intake of the National Institutes of Health, which recommended 1500 mg/d for estrogen-deficient, postmenopausal women. Although the dose of calcium and calcitriol for the study protocol was selected before current recommendations, the importance of calcium and calcitriol in older patients has been demonstrated in a number of studies.

Levels of 25-hydroxyvitamin D increased significantly in both groups, supporting a pharmacologic effect of calcitriol supplementation. However, the rise was small, and 25-hydroxyvitamin D levels remained within the normal range. Surprisingly, 1,25-dihydroxyvitamin D levels fell in both groups. The mechanism of the fall in 1,25-dihydroxyvitamin D level is not clear. Cholecalciferol toxicity has been shown to inhibit renal 1α-hydroxylase activity. The subtle decline in PTH level seems a possible but unlikely explanation for the fall in 1,25-dihydroxyvitamin D levels. Weisinger et al reported that 1,25-dihydroxyvitamin D levels are regulated by calcium independently of serum PTH in rats. Whether the decline in PTH levels or influence of supplemental calcium independently played a role in reducing 1,25-dihydroxyvitamin D levels in this study is speculative and would require further investigation.

Figure 2. Measurement of biochemical markers during the 42-month study. Data are given as mean (±SEM). PTH indicates parathyroid hormone; BSAP, bone-specific alkaline phosphatase; BCE, bone collagen equivalents; and SR-NaF, sustained-release sodium fluoride. Months 12 to 14, 26 to 28, and 40 to 42 represent 2-month periods free of study medication.
The results also demonstrate significant biochemical changes in markers of bone turnover and resorption in patients receiving only calcium citrate and cholecalciferol. A significant decline from baseline in urinary N-telopeptide and serum osteocalcin levels was seen in the control group, suggesting that bone turnover was reduced and resulting in the modest increase in bone mass at the spine and maintenance at the hip. These findings support the therapeutically effective antiresorptive action of the calcium and cholecalciferol.\textsuperscript{11,12} The pattern of decline in markers of bone turnover is similar to that of other antiresorptive agents.\textsuperscript{14-16,45}

However, the addition of a bone-forming agent (sustained-release sodium fluoride) to calcium and cholecalciferol mitigated the reduction in markers of bone turnover that was seen in the control group. As opposed to a reduction in BSAP response seen with estrogen or bisphosphonates, potent inhibitors of bone resorption, BSAP response increased and osteocalcin levels were maintained in the SR-NaF group. Furthermore, urinary calcium levels increased in both groups compared with baseline but significantly less in the SR-NaF subjects compared with controls. This finding may be related to increased calcium use by newly formed bone. The combination of a regimen of bone-forming (sustained-release sodium fluoride) and antiresorptive (calcium and cholecalciferol) agents proved effective in decreasing the vertebral fracture rate in this group of high-risk patients. Whether the addition of a more potent antiresorptive agent, such as a bisphosphate or estrogen, would have shown greater therapeutic efficacy is not known but would seem to be an appropriate avenue of future investigation. The small subgroup of patients already receiving estrogen did not appear to influence response to therapy.

The pattern of increased markers of bone turnover and formation has also been seen with other anabolic agents. When PTH was given with estrogen in postmenopausal women with osteoporosis, urinary N-telopeptide and serum osteocalcin levels transiently increased compared with an estrogen-only group.\textsuperscript{46} These findings suggest that anabolic bone agents such as fluoride and PTH may influence bone metabolism by increasing bone turnover via osteoblastic stimulation or recruitment, directly or indirectly. Since bone mass increases, a new resorption-formation coupling ratio seems to be established.

The results of this study are similar to those of an earlier study in which sustained-release sodium fluoride and calcium were given to postmenopausal women with established osteoporosis.\textsuperscript{23} The present study differs from that of Pak et al\textsuperscript{23} in that all patients in this trial received supplemental cholecalciferol (600 IU vs none) and a higher amount of supplemental calcium citrate (945 mg vs 800 mg). The mean age of patients was also somewhat older (73 vs 68 years), and they were exclusively aged 65 years or older in this trial.

Our findings support the use of sustained-release sodium fluoride with calcium and cholecalciferol in treating older ambulatory women with established osteoporosis. Our results suggest this combination of therapy safely reduces the risk for vertebral fractures by stimulating new bone formation by fluoride-mediated increased osteoblastic activity. In addition, the adequate provision of calcium and cholecalciferol reduces bone resorption. Therefore, this combination therapy addresses 2 fundamental abnormalities underlying the pathophysiology of age-related osteoporosis. Our findings also support investigations in the use of combining bone-forming and antiresorptive agents in the treatment of osteoporosis.

Accepted for publication March 29, 2001.

This work was supported by grants K08-AG00481 and M01-RR0633 from the National Institutes of Health, Bethesda, Md.


We wish to thank Ann Heard, RN, Elizabeth McDonald, RN, and the staff of the General Clinical Research Center, Dallas, Tex, for their invaluable assistance in performing this study; John Pointdexter for data management support; and Khashayar Sakhaee, MD, for x-ray visual determination.

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