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ORIGINAL CONTRIBUTIONS

A Prospective Study of Bone Mineral Content and Fracture in Communities with Differential Fluoride Exposure

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In 1983/1984, a study of bone mass and fractures was begun in 827 women aged 20–80 years in three rural Iowa communities selected for the fluoride and calcium content of their community water supplies. The control community's water had a calcium content of 67 mg/liter and a fluoride content of 1 mg/liter. The higher-calcium community had water with a calcium content of 375 mg/liter and a fluoride content of 1 mg/liter. The higher-fluoride community's water had 15 mg/liter of calcium and 4 mg/liter of fluoride naturally occurring. In 1988/1989, a follow-up study characterized the 684 women still living and available for study. Residence in the higher-fluoride community was associated with a significantly lower radial bone mass in premenopausal and postmenopausal women, an increased rate of radial bone mass loss in premenopausal women, and significantly more fractures among postmenopausal women. There was no difference in the 5-year relative risk of any fracture in the higher-calcium community versus the control community; however, the relative risk was 2.1 (95% confidence interval (CI) 1.0–4.4) in women in the higher-fluoride community compared with women in the control community. There was no difference in the 5-year risk of wrist, spine, or hip fracture in the higher-calcium community versus the control community; however, the 5-year relative risk for women in the higher-fluoride community, compared with women in the control community, was 2.2 (95% CI 1.1–4.7). Estimates of risk were adjusted for age and body size. *Am J Epidemiol* 1991;133:649–60.

bone and bones; calcium; fluoridation; fluorides; fractures

Because of the economic and health costs of fractures, loss of bone mass and osteoporosis are important aspects of quality of life. The lifetime risk of hip fracture is estimated to be 15 percent in women and 5 percent in men; this is equivalent to the lifetime risk of developing breast, uterine, or ovarian cancer in women and prostate cancer in men. The cost of health care associated with fractures in the United States was estimated to be $6.1 billion in 1984 (1, 2) and has been projected to be more than $100 billion by the year 2020 (3).

Estrogen replacement, calcium supplementation, and fluoride therapy have been proposed to prevent, minimize, or treat bone mass loss and fractures. Sodium fluoride therapy has been of particular interest because of its ability to stimulate bone formation (4). Clinical trials which have examined the effect of sodium fluoride on fractures have reported conflicting responses. For example, Inkovaara et al. (5) treated elderly nursing home residents with sodium monofluorophosphate or sodium bicarbonate and observed that 6 percent of the treated sub-

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Abbreviation: CI, confidence interval.

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jects subsequently had a fracture, while 3 percent of control subjects had a fracture. A 4-year trial conducted at the Mayo Clinic, Rochester, Minnesota, reported increased nonvertebral fractures and lower radial bone mineral density among subjects randomized to receive sodium fluoride therapy (6); however, there was a significant increase in bone mineral density of the lumbar spine and similar numbers of vertebral fractures in the treated and placebo groups. A 2-year trial in France reported a significantly lower vertebral fracture rate in the sodium fluoride treatment group; no data describing level of bone mineral density were provided (7). It has been suggested that fracture incidence may be minimal if the sodium fluoride is given in a timed-release preparation and/or in a different dose (8).

Studies of fluoride and fractures based on comparison of geographic areas with various levels of fluoride in their water supplies have generally reported no effect or a positive effect with fluoride consumption (9–18); a review of these types of studies was recently published (19). Typically, the highest fluoride level evaluated in community water supplies has been less than 2 mg/liter, and studies have been cross-sectional in design.

An exception to those studies of lower fluoride levels was our previously reported cross-sectional study (20) which found significantly more fractures in women living in a community with water fluoride levels of 4 mg/liter than in women in two other communities with fluoride levels of 1 mg/liter and vastly different calcium levels. This paper describes the 5-year incidence of fracture and bone mass in those three communities.

MATERIALS AND METHODS

Women living in three demographically similar rural communities in northwestern Iowa participated in a study of bone mass. The three communities were selected because the municipal drinking water supplies had divergent calcium and fluoride contents. The drinking water of the higher-fluoride community had a naturally occurring fluoride concentration of 4 ± 0.1 mg/liter (standard deviation) and an elemental calcium concentration of 15 ± 3 mg/liter; drinking water in the higher-calcium community averaged 375 ± 8 mg/liter of elemental calcium and was fluoridated to a level of 1 mg/liter. The third community, classified as the control community (21), had drinking water that was fluoridated at a level of 1 mg/liter and that had an average elemental calcium content of 67 ± 4 mg/liter. Inorganic constituents of these drinking waters were determined at the University of Iowa Hygienic Laboratory, the state public health laboratory, according to the most current methodologies (21). Mean mineral values for each community were generated from water sampling and testing that has occurred approximately every 5 years since 1938.

State-specific census data from 1970 and 1980 indicated that the communities were similar with respect to population size, age distribution, proportion foreign-born, mean income, and occupational categories. The population of each community was less than 2,000.

Women were eligible for the baseline study if they had lived in their respective communities for 5 years and if they consumed municipal water. Five years was arbitrarily selected as a time frame to allow sufficient incorporation of the minerals (22, 23). All participants were ambulatory, were not knowingly pregnant, and had not experienced wrist or forearm fractures in the previous 2 years which might bias measurement of radial bone mass. In the higher-fluoride community, participants were aged 20–80 years; in the other two communities, only women aged 20–35 years and 55–80 years were studied because of resource limitations. All eligible women were of northern European heritage, and there were no ethnic differences among the communities.

Eighty-nine percent (n = 417) of the eligible women completed the baseline study in the higher-fluoride community; 78 percent (n = 216) of the eligible women completed the baseline study in the higher-calcium community; and 77 percent (n = 194) of the eligible women completed the baseline study in the control community.

Information was gathered in the higher-fluoride community from May to August 1984 and in the other two communities from May to August 1983. Women who had participated in the baseline study were reexamined exactly 5 years after the initial study. To simplify presentation, we have labeled all data collected in 1983 or 1984 baseline data and all data collected in 1988 or 1989 follow-up data.

In the higher-fluoride community, 83.1 percent of women participated in the follow-up study; 2.2 percent had died, 8.2 percent had moved, and 6.5 percent refused reexamination. In the higher-calcium community, 85 percent of women participated in the follow-up study; 6.0 percent had died, 6.4 percent had moved, and 2.7 percent refused reexamination. In the control community, 81.5 percent of women participated in the follow-up study; 6.2 percent had died, 8.2 percent had moved, and 4.1 percent refused reexamination. These values were not significantly different between communities.

Bone mass measurement

Radial bone mass was measured at both time points by the method of Cameron and Sorenson (24) and Cameron et al. (25) using a Norland 278 photon absorptiometer (Norland Corporation, Madison, Wisconsin) with an iodine-125 source. Bone mass, expressed as the bone mineral:bone width ratio (g/cm^2), was measured distally at a site one third of the distance between the styloid process of the radius and the olecranon. The same procedure and instrumentation were used at both baseline and follow-up examinations. A single observer measured bone mass for all persons at baseline, while a different single observer measured bone mass at follow-up. Bone mass loss was calculated on an individual basis; women who were not participants at both baseline and follow-up were not included in bone mass loss calculations.

Femoral bone mass was measured, at follow-up only, using a Norland 2600 Dichromatic dual-photon densitometer with a gadolinum-153 source. Femoral bone mass was measured only in women who were no longer menstruating, were capable of reclining to a flat position, did not have hip pins, and were sufficiently lean to fit under the scanner arm ($n = 397$). Bone mass (g/cm^2) is reported for three femoral sites—the neck of the femur, Ward's triangle, and the trochanter—which include cortical and cancellous bone.

Other measurements

Interviewers recorded responses to questions about variables which may relate to bone mass. Fractures were recorded according to specific site and year of fracture. Fractures reported here are those fractures which occurred in the 5-year period between baseline and follow-up examinations in women who were participants at both times. Variables describing fracture were: likelihood that a woman had a fracture at any site versus no fracture; if fractured, likelihood of multiple fractures versus a single fracture; and, if fractured, likelihood of a fracture of the spine, hip, or wrist versus fractures at other sites.

At each time point, one trained observer measured each participant for height, weight, triceps skinfold thickness, and mid-arm circumference according to standardized procedures. Subjects were weighed in light clothing without shoes to the nearest 0.1 kg using an electronic scale; height was measured to the nearest 0.1 cm using an anthropometric plane and scale. Triceps skinfold thicknesses were measured with Lange calipers and recorded in millimeters using the mean of three consecutive readings; arm span and mid-arm circumference were measured with a steel tape to the nearest 0.5 and 0.1 cm, respectively. Quetelet index (weight (kg)/height $(m)^2$) was calculated from these measures.

Fluoride and nutrient intake assessment

Intake of water and water-based beverages was assessed using food frequency, 24-hour food recall, and water intake sections in the interview. Estimates of water intake from these methods were similar. A computer program was written which assigned calcium and fluoride values, on a community-specific basis, to water and water-based products such as frozen juice concentrates, powdered drink mixes, coffee, and tea. Calcium and fluoride intake values for liquids were assigned to an individual based on her report of the presence or absence and type of a home water-conditioning system. If an ion-exchange water conditioning system or bottled water was used in the higher-fluoride community, then a fluoride level of 0.3 ppm was assigned to beverages consumed by individuals who reported using these products (less than 20 percent of respondents). If water conditioning or bottled water use was reported in the higher-calcium community, a value of 60 mg/liter was assigned to beverages prepared with this conditioned or bottled water. We did not attempt to estimate calcium or fluoride ingested from foods prepared in large amounts of cooking water, such as rice.

Each participant was asked to recall her previous 24-hour intake of food during a face-to-face interview (26), as well as to respond to a food frequency questionnaire which characterized intake of foods high in calcium and vitamin D. Interviewers (five in the higher-fluoride community, two in the higher-calcium community, and two in the control community) were trained in appropriate techniques to solicit recall of food and beverage intake. The interviewers showed color photographs to each participant to enhance her recall of food serving sizes, which were reported and recorded in common household units. To promote accuracy, food and beverage intakes from each recall and the food frequency were coded independently twice. The correlation between calcium intakes as estimated by the two different methods was 0.56 at baseline and 0.64 at follow-up.

Nutrient values were assigned to coded foods and beverages using US Department of Agriculture food composition tape 456 (available from the National Technical Information Service, US Department of Commerce, Springfield, Virginia). This computer tape provides 20 nutrient values, including calcium, for more than 2,600 foods. The tape does not include values for vitamin D and fluoride; thus, a supplemental computer program was developed to assign vitamin D values to foods and beverages. These values were based on information from the food composition tables published in Southgate and Southgate's *McCance and Widdowson's The Composition of Foods* (27) or on other information sources about fortified products such as milk and dry cereals.

Fluoride values were not assigned to foods or to non-water-based beverages. The ionic or free form of fluoride in water can be tested with a fluoride-specific electrode, but no adequate methods are accepted for testing for the free and bound fluoride found in foods (28–34). On the basis of composite diet analysis, water is the primary source of fluoride (29). More than 80 percent of participants in the control and higher-calcium communities used toothpastes containing fluoride, while 39 percent of participants in the higher-fluoride community used these products; however, the amounts of these products used were not assessed, given the variety in practices associated with quantity of use, mouth rinsing, and expectoration of the rinse.

The interviewer gathered information about nutritional supplements by observing the labels of currently used preparations and asking the participant to recall the number, frequency, and individual duration of use of the preparations. We added these estimates of supplement use to nutrient intake from food and water to calculate total intake. Interviews also included information about estrogen replacement therapy, surgical menopause, and use of oral contraceptives.

Procedures followed were approved by the Universities of Michigan and Iowa Committees on Human Experimentation and their Radiation Protection Subcommittees.

Data analysis

Normality of variable distributions was evaluated with univariate analysis. Variables with skewed distributions were $\log_{10}$-

transformed (nutrient intakes) or categorized. Chi-square tests were used to determine whether the women of the communities were homogeneous with respect to ethnicity, occupation, marital status, and education. Analysis of covariance with Tukey multiple-comparison tests was used to generate and compare mean bone mass measurements and physical measurements by community.

Associations between levels of bone mass and community, controlling for age and Quetelet index, were tested using analysis of variance (35). Probabilities of fracture between baseline and follow-up in relation to community fluoride exposure, considering important covariates such as age, Quetelet index, calcium intake, vitamin D intake, and interactions, were evaluated using stepwise logistic regression analysis. Estimates of relative risk with their 95 percent confidence intervals were calculated from the beta coefficients and standard errors (36).

RESULTS

Bone mass measurements

The numbers of participants, ages, and Quetelet indexes of women in each of the three communities are shown in table 1 according to three major age groupings of 20–35 years, 36–54 years, and 55–80 years.

TABLE 1. Selected characteristics of women who participated at both baseline (1983/1984) and follow-up (1988/1989) in a study of water mineral characteristics, bone mass, and fractures, by age group and type of community water supply, rural Iowa

	Type of community water supply		
	Control	Higher-calcium	Higher-fluoride
	Women aged 20–35 years at baseline		
No. of participants	37	33	67
Age (years)			
Baseline	29.3 ± 4.0†	29.0 ± 4.1	29.8 ± 3.3
Follow-up	34.4 ± 4.1	34.0 ± 4.1	34.8 ± 3.4
Quetelet index‡			
Baseline	24.7 ± 6.2	23.5 ± 3.9	24.3 ± 4.7
Follow-up	26.0 ± 7.1	24.1 ± 4.2	25.0 ± 5.4
	Women aged 36–54 years at baseline§		
No. of participants			115
Age (years)			
Baseline			46.5 ± 5.5
Follow-up			51.4 ± 5.3
Quetelet index			
Baseline			26.9 ± 6.7
Follow-up			27.5 ± 6.2
	Women aged 55–80 years at baseline		
No. of participants	121	148	163
Age (years)			
Baseline	65.5 ± 7.3	67.1 ± 7.2	67.7 ± 6.7
Follow-up	70.6 ± 7.4	72.0 ± 7.2	72.6 ± 6.7*
Quetelet index			
Baseline	27.7 ± 4.9	28.2 ± 5.3	27.6 ± 5.3
Follow-up	27.5 ± 5.1	28.1 ± 5.4	27.3 ± 5.7

* $p < 0.02$.
† Mean ± standard deviation.
‡ Weight (kg)/height (m)^2.
§ No information was collected on women aged 36–54 years in the control and higher-calcium communities.

The only significant difference in these characteristics by community was mean age—that of women in the higher-fluoride community was approximately 1 year greater at follow-up than the mean ages of women in the higher-calcium and control communities. There were no significant differences by community in the distributions of estrogen replacement therapy, oral contraceptive use, frequency of surgical menopause, and estimated nutrients from diet and supplements.

Table 2 shows the comparisons of mean radial bone mass, by community, in young adult women, adjusted for age and Quetelet index. There were no significant differences by community in mean radial bone mass measurement at baseline. However, at follow-up, young women in the higher-fluoride community had significantly lower mean bone mass values than did women in the control ($p = 0.04$) and higher-calcium ($p = 0.02$) communities. Furthermore, the mean loss of radial bone, expressed as absolute difference or percentage of loss, was greater in women of the higher-fluoride community than in women of the control ($p = 0.08$) and higher-calcium ($p = 0.03$) communities.

The mean radial bone mass values, by community, for women in the 55- to 80-year age group are shown in table 3. The values are adjusted for age and Quetelet index. At baseline, mean radial bone mass was significantly lower in the higher-fluoride community than in the control ($p = 0.02$) and higher-calcium ($p = 0.006$) communities. A similar observation was made about women who participated in the follow-up study. The follow-up mean radial bone mass value was significantly lower in the higher-fluoride community than in the control ($p = 0.01$) and higher-calcium ($p = 0.003$) communities. Despite the lower mean radial bone mass values, the rates of change in radial bone mass were not significantly different among the communities during this 5-year period.

The mean bone mass of the femur consistently tended to be lower in the higher-fluoride community than in the higher-calcium community (table 4); however, the mean femoral bone mass measures were not significantly lower than mean values in the control community. Although women in the higher-calcium community had a higher mean femoral bone mass than the women

TABLE 2. Mean radial bone mass in women aged 20–35 years at baseline (1983/1984), by community, in rural Iowa communities with different water mineral characteristics

	Adjusted* value		p for difference in means
Baseline (1983/1984) radial bone mass (g/cm^2)			
Control ($n = 37$)	0.75 ± 0.008†		
Higher-calcium ($n = 33$)	0.75 ± 0.008		NS‡
Higher-fluoride ($n = 67$)	0.74 ± 0.006		
Follow-up (1988/1989) radial bone mass (g/cm^2)			
Control	0.73 ± 0.008		
Higher-calcium	0.74 ± 0.009	0.02	0.04
Higher-fluoride	0.71 ± 0.006		
Absolute difference in radial bone mass in 5 years (g/cm^2)			
Control	−0.015 ± 0.005		
Higher-calcium	−0.011 ± 0.005	0.03	0.08
Higher-fluoride	−0.027 ± 0.004		
% loss of radial bone mass in 5 years			
Control	−2.1 ± 0.7		
Higher-calcium	−1.6 ± 0.7	0.03	0.08
Higher-fluoride	−3.6 ± 0.5		

* Adjusted for age and Quetelet index (weight (kg)/height (m)^2).
† Mean ± standard error.
‡ NS, not significant.

TABLE 3. Mean radial bone mass in women aged 55–80 years at baseline (1983/1984), by community, in rural Iowa communities with different water mineral characteristics

	Adjusted* value	*p* for difference in means	
Baseline (1983/1984) radial bone mass (g/cm²)			
Control (n = 121)	0.63 ± 0.008†		
Higher-calcium (n = 148)	0.63 ± 0.007	0.006	0.02
Higher-fluoride (n = 163)	0.60 ± 0.007		
Follow-up (1988/1989) radial bone mass (g/cm²)			
Control	0.59 ± 0.008		
Higher-calcium	0.59 ± 0.007	0.003	0.01
Higher-fluoride	0.56 ± 0.007		
Absolute difference in radial bone mass in 5 years (g/cm²)			
Control	−0.039 ± 0.004		
Higher-calcium	−0.043 ± 0.003		NS‡
Higher-fluoride	−0.046 ± 0.003		
% loss of radial bone mass in 5 years			
Control	−6.4 ± 0.6		
Higher-calcium	−6.9 ± 0.5		NS
Higher-fluoride	−7.4 ± 0.5		

* Adjusted for age and Quetelet index (weight (kg)/height (m)²)
† Mean ± standard error.
‡ NS, not significant

TABLE 4. *Femoral bone mass among women in three rural Iowa communities with differences in the mineral content of their community water supplies*

	Adjusted* value	*p* for difference in means	
Femoral neck (g/cm²)			
Control (n = 110)	0.69 ± 0.011†		
Higher-calcium (n = 136)	*0.71 ± 0.009*	0.03	NS‡
Higher-fluoride (n = 151)	0.68 ± 0.009		
Trochanter (g/cm²)			
Control	0.65 ± 0.012		
Higher-calcium	0.65 ± 0.011	0.05	0.07
Higher-fluoride	0.63 ± 0.011		
Ward's triangle (g/cm²)			
Control	0.60 ± 0.012		
Higher-calcium	0.63 ± 0.011	*0.08* / 0.02	NS
Higher-fluoride	0.59 ± 0.011		

* Adjusted for age and Quetelet index (weight (kg)/height (m)²).
† Mean ± standard error
‡ NS, not significant.

in the control community, irrespective of site, the difference was not statistically significant.

Fractures

The distribution of fractures is shown in table 5 according to age group and within specific sites. The values for site-specific fractures do not total to values reported in the overall frequencies because some women experienced fractures at multiple sites but were counted only once as having had a fracture in the 5-year period.

Relative risk of fracture was calculated according to community, with estimates of risk adjusted for age and Quetelet index. As table 6 shows, among women in the 20- to 35-year age group, there was an increased probability of fracture in the higher-fluoride

TABLE 5. Five-year (1983/1984–1988/1989) fracture frequency in women of three rural Iowa communities with differences in the mineral content of their community water supplies, by age group and site*

Site of fracture	Age group (years)	Community		
		Control	Higher-calcium	Higher-fluoride
	20–35	3/37 (8)†	1/33 (3)	9/67 (13)
	36–54	—‡	—‡	10/115 (9)
	55–80	11/121 (9)	21/148 (14)	31/163 (19)
Hand	20–35	0/37 (0)	1/33 (3)	0/67 (0)
	36–54	—	—	0/115 (0)
	55–80	0/121 (0)	0/148 (0)	1/163 (1)
Arm	20–35	0/37 (0)	0/33 (0)	1/67 (1)
	36–54	—	—	2/115 (2)
	55–80	2/121 (2)	3/148 (2)	4/163 (2)
Wrist	20–35	0/37 (0)	0/33 (0)	1/67 (1)
	36–54	—	—	4/115 (3)
	55–80	2/121 (1)	5/148 (3)	10/163 (6)
Spine	20–35	0/37 (0)	0/33 (0)	0/67 (0)
	36–54	—	—	0/115 (0)
	55–80	0/121 (0)	0/148 (0)	3/163 (2)
Pelvis	20–35	0/37 (0)	0/33 (0)	0/67 (0)
	36–54	—	—	0/115 (0)
	55–80	0/121 (0)	1/148 (1)	2/163 (1)
Leg	20–35	1/37 (3)	0/33 (0)	1/67 (1)
	36–54	—	—	0/115 (0)
	55–80	0/121 (0)	0/148 (0)	2/163 (1)
Other	20–35	2/37 (5)	1/33 (3)	5/67 (7)
	36–54	—	—	6/115 (5)
	55–80	7/121 (6)	12/148 (8)	12/163 (7)
Hip	20–35	0/37 (0)	0/33 (0)	1/67 (1)
	36–54	—	—	1/115 (1)
	55–80	0/121 (0)	2/148 (1)	5/163 (3)

* Site-specific fractures (which includes multiple fractures) do not total to age-group fractures (which counts only individuals)
† Numbers in parentheses, percentage.
‡ Participants were not studied in these age groups in the control and higher-calcium communities.

TABLE 6. Risk of fracture in a 5-year period (1983/1984–1988/1989) among women of three rural Iowa communities with differences in the mineral content of their community water supplies, by age group and community

Community	Relative risk* (95% confidence interval)		
	Any fracture	Fracture of hip, wrist, or spine	Fractures at multiple sites
	Women aged 20–35 years at baseline†		
Control	—‡	—	
Higher-calcium	0.36 (0.03–3.63)	0.30 (0.04–3.39)	
Higher-fluoride	1.81 (0.45–8.22)	2.70 (0.16–8.28)	
	Women aged 55–80 years at baseline		
Control	—	—	—
Higher-calcium	1.54 (0.70–3.37)	1.60 (0.71–3.40)	1.60 (0.71–3.41)
Higher-fluoride	2.11 (1.01–4.43)§	2.20 (1.07–4.69)	2.20 (1.04–4.57)

* Adjusted for age and Quetelet index (weight (kg)/height (m)^2).
† There were no multiple fractures in this age group.
‡ Referent.
§ Relative risk adjusted for baseline radial bone mass = 1.99 (95 percent confidence interval 0.95–4.20).

community as compared with the referent community; however, the confidence interval included 1. There was also an increased risk of fracture at the spine, hip, or wrist; however, again, the confidence interval included 1.

In the 55- to 80-year age group, there was no significant difference in the 5-year fracture relative risk between the higher-calcium community and the control community; however, in the higher-fluoride community, there was an increased relative risk of 2.1 (95 percent confidence interval (CI) 1.0–4.4) compared with the control community. There was no significant difference in the 5-year risk of fracture occurring at the wrist, spine, or hip in the higher-calcium community versus the control community; however, the 5-year risk in the higher-fluoride community compared with the control community was 2.2 (95 percent CI 1.1–4.7). There was no significant difference in the 5-year risk of multiple fractures between the control community and the higher-calcium community; however, in the higher-fluoride community, there was an increased relative risk of 2.2 (95 percent CI 1.0–4.6) for multiple fractures.

When individual total calcium or vitamin D intakes estimated from either diet instrument were added to the logistic regression model to adjust for the variability of nutrient intake in the communities, there was no difference from the relative risks described above. Furthermore, when the probability of fracture was adjusted for the baseline radial bone mass value, women aged 55–80 years living in the higher-fluoride community continued to have an increased risk of fracture relative to women of the same age in the control community (relative risk = 1.99, 95 percent CI 0.95–4.21).

Within the higher-fluoride community, fluoride dose, expressed as the reported years of residence multiplied by estimated daily fluoride intake from beverages, was positively associated with risk of fracture. Upon further examination, it was observed that the relative risk of fracture in postmenopausal women with a fluoride exposure less than the median was 1.9 (95 percent CI 0.88–4.0), while those postmenopausal women with an exposure greater than the median had a relative risk of 2.6 (95 percent CI 1.2–6.0) when compared with premenopausal women. These relative risks were adjusted for age and Quetelet index.

DISCUSSION

A recent clinical trial (6) observed that although women with osteoporosis had a significantly increased vertebral bone mineral density when treated with sodium fluoride, there was no concordant decline in vertebral fracture. Furthermore, there was an unexpected increase in the number of appendicular fractures in the treated group as compared with controls. Based on findings from this trial and the increasing cost of conducting multiple trials to determine optimal doses and delivery systems (6), it appears that studies of geographic differences in fluoride consumption can still contribute to our understanding of fluoride's role in bone mineralization and bone architecture.

Greater relative loss of radial bone mass among women in the higher-fluoride community than in women in the control and higher-calcium communities appears to be established prior to age 55. In the women who were aged 20–35 years at baseline, there was apparently greater bone mass loss in the higher-fluoride community. The apparent loss of bone mineral density in the younger women residing in the control and higher-calcium communities is within the measurement error of the single-photon densitometer; however, the loss in the higher-fluoride community exceeded the ±2 percent measurement error. This was particularly prominent in women who were aged 25–29 years at baseline. We could determine no reason, apart from the higher fluoride exposure, why women in the higher-fluoride community should have greater loss of bone mass than women in the other two communities. When considering possible explanations, we found the women to have the same mean body size, the same frequency of oral contraceptive use, and similar calcium intakes as young adult women in the control community. There were no more young adult women in the higher-fluoride community who had had a premature or surgical menopause than in the other two communities. Furthermore, young adult women who moved away from the higher-fluoride community ($n = 18$) did not have significantly higher baseline bone densities than the young adult women who remained.

Lower radial bone mass was evident among the women aged 55–80 years at baseline in the higher-fluoride community; however, prospective evaluation indicated that these older women lost bone mass at approximately the same rate, over 5 years, as women in the control and higher-calcium communities. Unfortunately, the lack of bone mass and fracture data in the midlife age interval for the control and higher-calcium communities prevented us from comparing factors associated with estrogen status. These comparisons might have included frequency of perimenopausal estrogen supplementation or follicle-stimulating hormone determinations to describe the differences in hormonal characteristics around the menopause. We were able to determine that there was no difference in the mean age of reported menopause between communities. The values were 46.9 years in the control community and 47.9 years in the higher-fluoride community ($p = 0.33$). The participants from the higher-fluoride community used perimenopausal estrogens with the same frequency as women in the other two communities. The mean numbers of years of perimenopausal estrogen use and years since last use were similar in the three communities.

The rationale for an increased risk of fracture in the higher-fluoride community has not been fully developed in relation to bone mineral content. For example, the recent clinical trial at the Mayo Clinic reported increased appendicular fractures in spite of greater vertebral bone mass (6). Ruegsegger et al. (37), using computerized tomography, reported a gain in cancellous bone but a loss of cortical bone, suggesting a redistribution of bone mineral rather than additional mineralization. Increased fluoride exposure, in the presence of minimal calcium and vitamin D intake, is associated with a defect in the mineralization of bone which may include increased crystallinity and decreased elasticity (38, 39). We observed that an important increase in risk of fracture was observable in the higher-fluoride community even after controlling for the radial bone density measured at baseline. Additional longitudinal information from other skeletal sites would be helpful in understanding the role of bone mass.

Although there have been multiple geographic studies of bone and fluoride exposure, the majority of these have tended to characterize bone mass and fracture in populations where the water supply contained 2 mg/liter of fluoride or less (9–16). Several studies have examined higher doses. Early studies of fluoride and bone began in the 1950s and 1960s with radiographic evidence suggesting less osteoporosis in communities with higher fluoride exposure as compared with communities with lower fluoride exposure (40–42). Unfortunately, the study populations were not well-characterized as to ethnicity, age, sunlight exposure, and other factors which might confound such a relation. A study by Bernstein et al. (17) in North Dakota reported decreased radiographic bone density and more frequent collapse of vertebrae in women residing in a low-fluoride area (<0.3 mg/liter) as compared with women in a higher-fluoride (4–5.8 mg/liter) area. However, men were observed to have more collapsed vertebrae than women, and the frequency of collapse in men was not associated with type of water consumed.

Our observations may be related either to fluoride exposure or to other unique but unknown factors associated with these three communities. In an earlier report (20) of a cross-sectional study in these communities, we described more fractures observed in participants from the higher-fluoride community. The prospective observation that there was greater fracture incidence in a 5-year period suggests that the observation of increased fractures is not an artifact. The increased incidence of fractures in young adult women, though not statistically significant, suggests that the observation among older women is also not an artifact or the function of a specific age cohort.

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