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Effects of a low sodium diet on bone metabolism

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Abstract Osteoporosis is a serious public health problem, and dietary interventions may potentially be helpful in preventing this disorder. The purpose of this study was to determine the effects of a low sodium diet on bone metabolism in postmenopausal women. This was a longitudinal study to determine the effects of a low sodium (2-g/day) diet on bone. Forty postmenopausal African–American and Caucasian women were enrolled in a 2-g/day sodium diet for 6 months. Sodium and calcium excretion, bone turnover, and calcitropic hormones (intact parathyroid hormone (PTH) and 1,25 dihydroxyvitamin D) were measured before and 6 months after the intervention. In women who had baseline sodium excretions equal to or greater than the average sodium intake in the United States (≥3.4 g/day), the low sodium diet resulted in significant decreases in sodium excretion ($P = 0.01$), in calcium excretion ($P = 0.01$), and in a biomarker of bone turnover, aminoterminal propeptide of type I collagen ($P = 0.04$). However, there were no significant changes in calcitropic hormones, including intact PTH ($P = 0.97$) or 1,25 dihydroxyvitamin D ($P = 0.49$) with the low sodium diet. These findings suggest that in postmenopausal women with sodium intakes ≥3.4 g/day, a low sodium diet may have benefits for skeletal health.

Key words Diet · Sodium · Bone

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Introductions

In the United States, during the last few decades, there has been a shift in dietary habits, with an increased consumption of processed and fast foods which are high in sodium [1]. However, the public health implications of high sodium intakes have largely focused on cardiovascular endpoints alone, and have not sufficiently examined the implications for other organ systems. In addition, the role of nutrition on skeletal health is often underappreciated until later in life, when lifetime dietary habits begin to have a greater impact [2].

The role of calcium in the prevention and treatment of osteoporosis is well established [3,4], but less emphasis has been placed on the factors that may modulate calcium availability, specifically, sodium. In a recent study we found that there was an association between sodium and calcium excretion, particularly at low calcium excretions [5]. Others have also documented a relationship between sodium and calcium excretion [6,7], and it has been postulated that the mobilization of calcium stores could constitute a risk factor for osteoporosis [7].

The results of epidemiological studies examining the relationship of sodium to osteoporosis are conflicting [6,8]. Some studies have reported no effect of sodium excretion on bone mass [8], while others have suggested a negative correlation of sodium excretion with bone mass [6]. One longitudinal study reported that there is a significant association between higher sodium excretion and greater bone loss in postmenopausal women, although this study was not designed to determine the effects of lowering sodium excretion on bone [9]. Previous studies that have examined the relationship of a low sodium diet to bone metabolism are limited by the very short duration of these trials, and the failure to assess sodium intake adequately [9–11].

Reductions in dietary sodium excretion may decrease blood pressure [12,13], and some populations are particularly sensitive to the effects of sodium on blood pressure [14,15]. Processed foods, which are high in sodium [16], are usually also calorie-dense, but the effects of

reduced sodium diets on body weight have not been adequately studied.

Materials and methods

The purpose of this longitudinal study was to determine the effects of a 6-month low sodium (2-g/day) diet on sodium and calcium excretion, biomarkers of bone turnover, and calcitropic hormones (intact parathyroid hormone (PTH) and 1, 25 dihydroxyvitamin D) in postmenopausal African–American and Caucasian women.

Subjects

Subjects included postmenopausal African–American and Caucasian women who were at least 5 years past the menopause and between the ages of 55 and 85. Exclusion criteria included a history of congestive heart failure, uncontrolled hypertension, nephrolithiasis, renal disease, hyperthyroidism, cancer, primary hyperparathyroidism, rheumatoid arthritis, Cushing's disease, and gastric resection. Subjects were also excluded if they reported using diuretics, supplemental calcium (>1000 mg/day), estrogen, corticosteroids, or anticonvulsants within 6 months of the study, or reported ever having used raloxifene, bisphosphonates, or calcitonin. Written consent for participation in the study was obtained from all participants in accordance with the Helsinki II declaration, and the protocol was approved by the University of Tennessee Health Science Center Institutional Review Board.

Fifty-seven subjects were enrolled in the study, and 40 completed the entire 6 months. Seventeen women did not complete the 6-month study. Of these, 14 withdrew because they did not wish to comply with the urine collections or the low sodium diet, two withdrew owing to adverse events not felt to be study-related (intercurrent renal insufficiency and thoracic compression fracture), and one was lost to follow-up.

Measurements

Measurement of biomarkers

Blood and urine were collected after an overnight fast and analyzed in batches at the conclusion of the study. The aminoterminal propeptide of type I collagen (P1NP) (DiaSorin, Stillwater, MN, USA), a marker of bone formation, was measured in the serum by radioimmunoassay; N-telopeptide (NTX), a marker of bone resorption, and creatinine were measured in the urine (second morning void) by ELISA (Ostex International, Seattle, WA, USA, and Metra Biosystems, Mountain Home, CA, USA, respectively). All specimens were measured in duplicate, and the mean value was recorded.

In our laboratory, the intraassay coefficients of variation for P1NP, NTX, and creatinine are 2.68%, 1.35%, and 3.29%, respectively. The interassay coefficients of variation for these measurements are 2.56%, 1.48%, and 3.10%, respectively.

Measurement of calcitropic hormones

All serum samples were collected after an overnight fast and analyzed in batches at the conclusion of the study. Serum parathyroid hormone (PTH) was measured by chemiluminescence (Nichols, San Juan Capistrano, CA, USA). The intraassay coefficient of variation for PTH was 5.4%, with an interassay coefficient of variation of 6.0%.

Serum 1,25 dihydroxyvitamin D was measured by radioimmunoassay after column chromatography (Diasorin, Stillwater, MN, USA). The intraassay coefficient of variation ranged from 9.7% to 14.1% (depending on 1,25 D3 level), with an interassay coefficient of variation ranging between 14.7% and 21.4% (depending on 1, 25 D3 level).

Physical activity questionnaire

The Yale Physical Activity Scores (YPAS) of the participants were measured by interviewer-administered questionnaires. The YPAS has been validated in an elderly population and correlates significantly with VO2max. The YPAS has been evaluated for reliability through repeat administration in 76 subjects given 2 weeks apart. Test–retest correlations for the total time and energy expenditure were 0.57 and 0.58, respectively. Correlations ranged between 0.42 and 0.65 for the summation indices [17].

Blood pressure

Systolic and diastolic blood pressure was measured using a standard mercury sphygmomanometer after the participant had been seated for at least 5 min. Mean arterial pressure was calculated by standard measures [18].

Height and weight

Height was assessed using a Harpenden stadiometer, weight (without shoes) was determined using a calibrated balance scale, and body mass index (BMI) was calculated.

Measurement of bone mineral density (BMD)

During the course of this study, we changed DXA machines at our center twice, resulting in some participants being measured on different machines. We could not adequately assess the longitudinal changes in bone mineral density (BMD) using different DXA machines, but BMD was not used as an outcome measure in this study. The BMD of the total hip was measured at baseline only using a Lunar Prodigy, Hologic QDR 2000, or a Hologic Discovery. Standardized BMD was calculated with reference to the NHANES III Caucasian normative database [19].

Measurement of covariates

The participant's age, race, current smoking status, and family history of osteoporosis were derived from a self-administered questionnaire.

Assessment of sodium excretion

Eight 24-h urine collections for sodium, calcium, and creatinine were carried out over 1 month with the participant continuing on her usual diet prior to the dietary intervention. These eight collections of sodium excretions were averaged to determine each subject's baseline sodium intake. One 24-h urine collection for sodium and calcium excretion was done monthly as a check of compliance with the low sodium diet. At the end of the low sodium diet (but while the participant was still on the diet), eight 24-h urine collections for sodium, calcium, and creatinine were carried out to assess the response to the 2-g/day sodium diet. Participants were given detailed verbal and written instructions on how to collect a complete 24-h urine sample properly, and the time and volume of collections were recorded. The 24-h urine sodium was measured using an ion-selective electrode, 24-h urine creatinine was done by the Jaffe reaction (picric acid), and 24-h urine calcium was measured by o-cresolphthalein. The intraassay coefficients of variation for these 24-h urine specimens were 0.3%–1.6% (sodium), 0.6%–1.5% (creatinine), and 0.3%–2.3% (calcium). The interassay coefficients of variation were 1.1%–2.7%, 2.5%–3.2%, and 0.9%–1.2%, respectively. Any 24-h urine sample with a urine creatinine <0.65 mg/dl was excluded from the analysis.

Intervention: implementation of the low sodium diet

Participants were instructed in the 2-g/day sodium diet by a registered dietitian. On average, the dietitian met with the participants monthly and instructed them on product label reading, gave tips for dining out on the low sodium diet, and gave suggestions for the use of herbs and spices as salt alternatives. Sample food preparation (to determine palatability and preferences) was done. Monthly phone calls to encourage adherence to the diet were also performed by the dietitian. Each diet was tailored to the individual's specific food preferences.

Statistical analyses

Statistical analysis was performed using the SAS System for Windows (SAS Institute, Cary, NC, USA, version 9.1). Baseline sodium excretion was calculated as the mean of the eight baseline collections of 24-h urine sodium excretion, and the effects of the 2-g/day sodium diet on sodium excretion, calcium excretion, biomarkers, and calcitropic hormones after the 6-month 2-g/day sodium diet were determined (paired *t*-test). The participants were stratified into two groups based on baseline sodium excretion (<3.4 g and ≥3.4 g/sodium/day). We chose these cut-off points to determine the effects of a low sodium diet on women at or above the mean estimate for sodium intake of the adult US population compared to those with sodium intakes below the population mean; these cut-off points do not include discretionary sodium added to cooking or at the table [20]. Paired *t*-tests were also carried out to determine the effects of the 2-g/day sodium diet on changes in blood pressure and body weight.

Results

Table 1 shows the baseline characteristics of our study population. Both African–American and Caucasian postmenopausal women (mean age 63 years) were included. On

Table 1. Baseline demographic characteristics of the study population (*N* (%) or mean ± SD (range))

Characteristic	<3.4 g Baseline sodium excretion group ($n = 29$)	≥3.4 g Baseline sodium excretion group ($n = 11$)	*P* value (difference between groups)
Race			0.53
Caucasian	18 (62%)	8 (73%)	
African–American	11 (38%)	3 (27%)	
Age (years)	63.9 ± 7.0 (56.0–77.9)	62.2 ± 4.9 (55.9–71.2)	0.47
Years postmenopausal	19.0 ± 10.0 (5.1–39.7)	18.8 ± 9.0 (6.5–32.0)	0.96
Height (cm)	162.1 ± 6.5 (152.7–180.9)	162.7 ± 6.0 (152.5–172.0)	0.79
Weight (kg)	75.3 ± 15.7 (45.2–106.0)	75.5 ± 11.3 (60.5–92.7)	0.97
BMI (kg/m^2)	28.6 ± 5.5 (19.0–40.7)	28.7 + 5.8 (20.5–39.7)	0.94
Current smoking status	2 (7%)	0 (0%)	0.38
Family history of osteoporosis	7 (25%)	3 (27%)	0.89
BMD of total hip (g/cm^2)	0.920 ± 0.138 (0.684–1.190)	0.947 ± 0.203 (0.753–1.348)	0.62
Hip T score	–0.6 ± 1.1 (–3.1–1.1)	–0.3 ± 1.1 (–1.5–1.8)	0.49
Yale physical activity survey			0.65
0–<3 METS	14 (48%)	7 (64%)	
3–6 METS (moderate)	14 (48%)	3 (27%)	
>6 METS (vigorous)	1 (4%)	1 (9%)	

BMI, body mass index; BMD, bone mineral density

Table 2. Sodium excretion and calcitropic hormones from baseline to 6 months stratified by baseline sodium excretion (mean (SD))

	n	Baseline	6 Months	*P* value
Sodium excretion (mmoles/g creatinine)				
<3.4 g Baseline sodium excretion	29	112.93 (23.17)	100.22 (24.33)	0.01
≥3.4 g Baseline sodium excretion	11	174.98 (25.25)	124.77 (48.32)	0.01
PTH (pg/ml)				
<3.4 g Baseline sodium excretion	29	58.55 (23.27)	58.45 (22.96)	0.97
≥3.4 g Baseline sodium excretion	11	62.00 (32.32)	68.82 (28.77)	0.32
1,25 dihydroxyvitamin D (pg/ml)				
<3.4 g Baseline sodium excretion	29	39.24 (21.43)	32.66 (13.03)	0.07
≥3.4 g Baseline sodium excretion	11	43.64 (19.49)	40.82 (16.82)	0.49

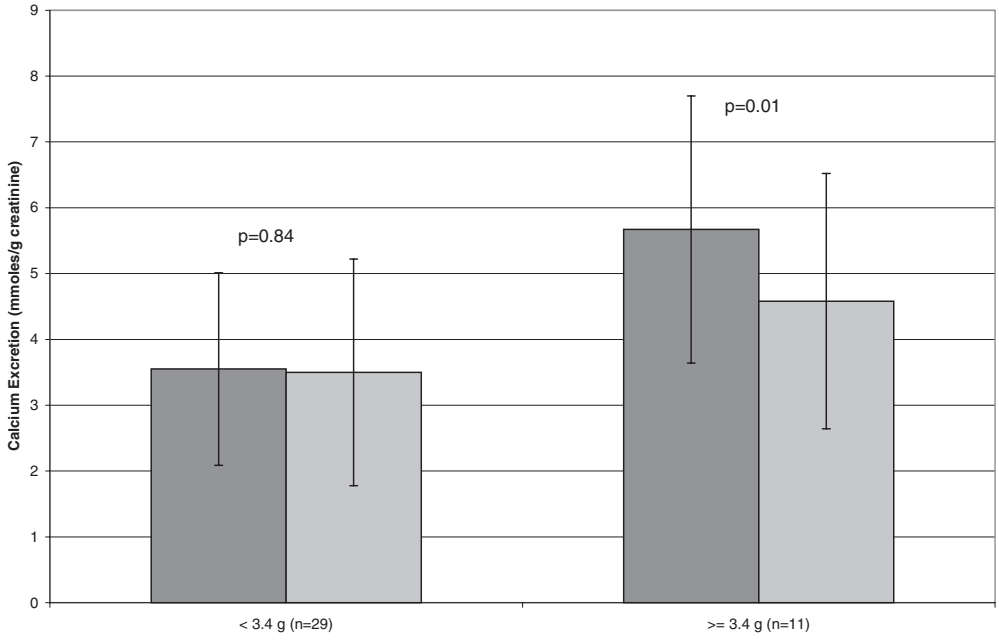

Fig. 1. Calcium excretion at baseline and 6 months by baseline sodium excretion. *Dark shading*, baseline; *light shading*, 6 months

average, these participants had normal BMD of the total hip, were overweight, and did not exercise vigorously [21]. Only one patient was currently a smoker, and approximately 26% had a family history of osteoporosis. There were no significant differences between those with a baseline sodium excretion of <3.4 g/day and those with a sodium excretion of ≥3.4 g/day with respect to race, age, years postmenopausal, BMI, smoking status, BMD of the total hip, and physical activity levels (Table 1). There was no significant correlation between baseline sodium excretion and BMD of the total hip ($P = 0.65$, data not shown).

In those participants with a baseline sodium excretion of ≥3.4 g/day, the low sodium diet resulted in a significant decrease in sodium ($P = 0.01$) (Table 2) and calcium excretion ($P = 0.01$) (Fig. 1) and P1NP ($P = 0.04$) after 6 months (Fig. 2A), with no significant decreases in NTX excretion ($P = 0.30$) (Fig. 2B). After every month of the study, sodium and calcium excretion were lower than the mean baseline value in those participants with a baseline sodium excretion ≥3.4 g/day (Table 3). There were no significant changes in intact PTH ($P = 0.97$) or 1,25 dihydroxyvitamin D ($P = 0.49$) with the 2-g/day sodium diet in this group (Table 2). No significant changes in sodium or calcium excretion, biomarkers, or calcitropic hormones occurred in those with a baseline sodium excretion <3.4 g/day (Table 2, Figs. 1 and 2). In those with a baseline mean sodium excretion <3.4 g/day, sodium excretion was lower than baseline in every month of the study, and calcium excretion was lower than baseline in months 1, 2, 5, and 6. Mean arterial pressure decreased in the low (<3.4 g/day) ($P = 0.02$), but not in the high (≥3.4 g/day) ($P = 0.69$), sodium excretion groups (Table 4). There was a statistically significant decrease in body weight in the low ($P < 0.01$), but not in the high ($P = 0.51$), baseline sodium group (Table 4).

Discussion

The major finding of our study is that a low sodium diet (2 g/day) has potential effects on skeletal health, but that these effects are a function of baseline sodium excretion. In those with a baseline sodium excretion equal to or greater than

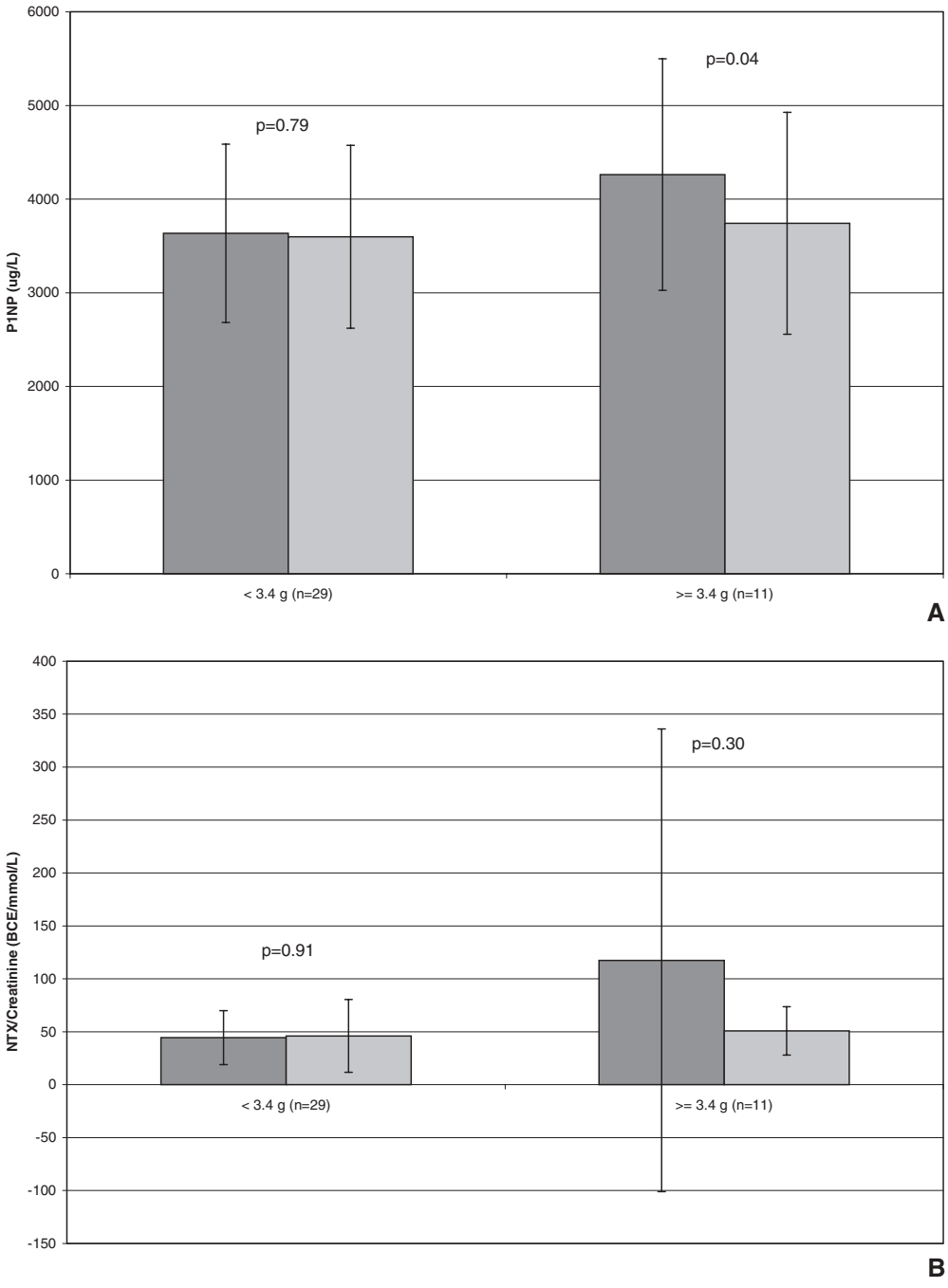

Fig. 2. **A** Propeptide of type 1 collagen (*P1NP*) at baseline and 6 months by baseline sodium excretion. **B** N-telopeptide (*NTX*)/creatinine at baseline and 6 months by baseline sodium excretion. *Dark shading*, baseline; *light shading*, 6 months

that of the average US population [20] (≥3.4 g/day), there were significant decreases in many skeletal parameters, including sodium and calcium excretion, and in a biomarker of bone turnover.

It is well established that increases in sodium excretion increase sodium and calcium excretion [6,7], and it is possible that this could constitute a risk factor for osteoporosis [7]. The importance of hypercalciuria as a risk factor for low bone mineral density has been reported in patients with idiopathic hypercalciuria [22–24]. In the Dietary Approaches to Stop Hypertension (DASH) study [25], significant decreases in urinary calcium excretion occurred with a low sodium diet. In another report, which was similar to our study, there was a differential effect of baseline sodium excretion on the response of calcium excretion to a low sodium diet, as only those participants with a sodium-to-creatinine ratio greater than 15 had significant decreases in calcium excretion [11]. Our study differs from others [11,12] in that it is the first to utilize multiple measurements of both sodium and calcium excretion, and it is considerably longer in duration than any study reported to date examining the effects of a low sodium diet on bone parameters. The importance of collecting multiple specimens of 24-h urine sodium cannot be overestimated. It has been suggested that optimally nine, and not just one, 24-h urine collections are needed for a reliable estimate of sodium intake in free-living people [26], although, in every study to date except ours, only one collection of 24-h urine sodium was done.

Table 3. Sodium and calcium excretion by month of study stratified by baseline sodium excretion (mean (SD))

	Baseline	1 Month	2 Months	3 Months	4 Months	5 Months	6 Months
Sodium excretion (mmoles/g creatinine)							
<3.4 g Baseline sodium excretion	112.93 (23.17)	83.79 (40.08)	87.44 (29.02)	101.12 (37.27)	90.88 (27.29)	102.65 (52.72)	100.22 (24.33)
≥3.4 g Baseline sodium excretion	174.98 (25.25)	112.89 (43.00)	118.54 (34.18)	99.55 (50.02)	136.45 (57.93)	122.19 (50.02)	124.77 (48.32)
Calcium excretion (mmoles/g creatinine)							
<3.4 g Baseline sodium excretion	3.55 (1.46)	3.39 (1.82)	3.36 (1.63)	3.96 (1.96)	3.71 (1.89)	3.52 (1.89)	3.50 (1.72)
≥3.4 g Baseline sodium excretion	5.67 (2.03)	5.07 (2.32)	4.84 (2.28)	5.01 (2.41)	5.59 (2.70)	5.27 (2.10)	4.58 (1.94)

The duration of the low sodium intervention is also important, as in order to have sustained benefits on bone health, one would expect that long-term adherence to such a dietary pattern would be important.

Bone turnover markers, including markers of bone formation and bone resorption, are associated with fracture risk [27–29] and are useful tools to monitor the response to an intervention [28,29]. In one study, hydroxyproline, a marker of bone resorption, was correlated with fasting sodium excretion in postmenopausal Caucasian women [6], although problems in the measurement of hydroxyproline limit its use as a specific marker of bone resorption [30]. Few studies have examined the impact of salt restriction on biomarkers of bone turnover. In a study of 59 postmenopausal women, the hydroxyproline/creatinine ratio fell from 18.2 to 16.8 after 1 week of sodium restriction (range of sodium restriction 50–80 mmoles/day), although in a similar way to our data, to achieve consistent decreases in this biomarker, the initial sodium-to-creatinine ratio had to be greater than 15 [8]. In another study of varying low sodium excretions for 3 months (50, 100, or 150 mmoles/day), bone turnover was not affected in the group assigned to the low sodium intervention alone. However, the low sodium diet was maintained for considerably less time in that study than in ours [10]. In contrast, we found a significant effect of the low sodium diet on lowering bone turnover in those with a baseline sodium excretion ≥3.4 g/day as assessed by P1NP. There was no decrease in the N-telopeptide/Cr ratio, and it is likely that P1NP is a more sensitive marker of changes in bone turnover than is N-telopeptide excretion [31] with this dietary intervention. This reduction in bone turnover is potentially of large clinical significance, as decreases in bone turnover with antiresorptive agents have been shown to be a major mechanism by which these agents impact on fracture risk reduction [32].

In our study, there were no significant changes in calcitropic hormones, including intact PTH and 1,25 dihydroxyvitamin D, with the low sodium diet. The response of PTH to changes in sodium excretion is controversial, with some [10,33,34], but not all [9,35], studies suggesting that PTH increases with higher sodium excretions to compensate for urinary calcium losses. It is possible that we missed some clinically important effects on PTH with the low sodium diet in view of the very short half-life of PTH [36]. In addition, although nine African–Americans and six Caucasians had elevations in intact PTH in our study, this was all due to secondary, not primary, hyperparathyroidism, and is in accord with data which suggests that secondary hyperparathyroidism is common in African–Americans [37]. Increases in 1,25 dihydroxyvitamin D in response to high salt diets have been reported [34,38]; to our knowledge, no previous study has examined the role of dietary restriction of sodium on 1,25 dihydroxyvitamin D levels. Our results suggest that intact PTH and 1,25 dihydroxyvitamin D are not modulated by decreases in sodium excretion.

There are several limitations to our study. Baseline sodium excretion was relatively low (mean 3.01 ± 0.87 g, range 1.34–5.16 g), and it is possible that compliance with the low

Table 4. Body weight and blood pressure from baseline to 6 months stratified by baseline sodium excretion (mean (SD))

	n	Baseline	6 months	*P* value
Systolic blood pressure (mm Hg)				
<3.4 g Baseline sodium excretion	29	129.2 (16.3)	122.8 (14.2)	0.04
≥3.4 g Baseline sodium excretion	11	127.3 (19.8)	128.2 (15.8)	0.85
Diastolic blood pressure (mm Hg)				
<3.4 g Baseline sodium excretion	29	80.4 (9.6)	76.3 (9.4)	0.03
≥3.4 g Baseline sodium excretion	11	77.6 (6.7)	75.8 (8.4)	0.29
Mean arterial pressure (mm Hg)				
<3.4 g Baseline sodium excretion	29	96.7 (10.8)	91.8 (10.0)	0.02
≥3.4 g Baseline sodium excretion	11	94.2 (10.2)	93.3 (10.2)	0.69
Weight (kg)				
<3.4 g Baseline sodium excretion	29	75.3 (15.7)	72.9 (15.4)	<0.01
≥3.4 g Baseline sodium excretion	11	75.5 (11.3)	77.3 (11.6)	0.51

sodium diet may have been more difficult in participants accustomed to higher sodium excretions. In fact, our sample size was unequal between the two groups (≥3.4 g sodium/day, $n = 29$; <3.4 g sodium/day, $n = 11$) because we were unable to recruit subjects with higher sodium intakes who were interested in participating in this study. However, based on our data, one would also have expected greater effects of the low sodium intervention on bone had baseline sodium excretion been higher. In addition, our experimental design did not include a control group undergoing no dietary interventions, which would have strengthened our conclusions. Baseline sodium excretion was not significantly correlated with BMD of the total hip, but our study was not adequately powered for this endpoint, and future studies of this aspect would be important. We did not measure serial BMDs to assess the response to the low salt diet because the intervention occurred within the transient bone remodeling phase for this population [39], and one would not have expected to see changes in BMD within the 6-month interval of our study. Our population was free-living, and except for changing their sodium intake, we did not control dietary calcium, protein, potassium, or phosphorus intake, all of which may potentially affect bone [40–45]. Furthermore, 24-h dietary recalls to assess potential changes in these nutrients were not collected. The small decreases in weight in the participants in this study were more likely to reflect changes in volume status than in body composition. In addition, there may be seasonal variations in bone markers, and our markers were collected at different times of the year [46]. However, in a recent study, the two bone markers used in our study (P1NP and NTX/creatinine) showed no seasonal variation [47]. Blood pressure decreased only in those participants with a baseline sodium excretion <3.4 g/day, suggesting that not all of our participants were "salt-sensitive" with respect to blood pressure, and that the responses to reductions in blood pressure with a low sodium diet are independent of the responses of bone turnover. We did not assess acid/base status, which may be altered by sodium intake [48] and has been reported to affect both bone turnover and BMD [49]. Finally, we included both African–Americans and Caucasians in our study, and there are known differences in bone metabolism between these groups [37], but our sample size of only three African–Americans in the baseline sodium excretion group of ≥3.4 g sodium/day precludes any meaningful analysis of potential differences in racial responses to the low sodium diet.

A 2-g/day sodium diet is inexpensive, has positive effects on bone metabolism in populations whose baseline sodium excretion is at or above the current US average excretion, and is close to the target sodium excretion recommended for the prevention of hypertension (<2.2 g sodium/day) [50]. Healthy People 2010 calls for a 50% reduction in sodium in the nation's food supply over the next 10 years [51]. Additional trials using other populations (including men and younger individuals) and outcomes including BMD are needed before routine recommendations concerning a reduced sodium diet can be made for bone health.

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