Original Article

Association between dietary selenium intake and bone mineral density in the US general population

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Background: Osteoporosis, characterized by reduced bone mineral density (BMD) increases the risk of all-cause mortality. Assessments of whether dietary selenium intake is related to bone health are scarce, with few relevant studies limited by a small sample size. The aim of the present study was to investigate the association between dietary selenium intake and BMD levels in the National Health and Nutrition Examination Survey (NHANES) database.

Methods: We extracted and aggregated data from 4 cycles of the NHANES [2005–2010, 2013–2014]. Dietary selenium intake was obtained from 24-hour dietary recall interviews. BMD measurement, including the femur, femur neck, trochanter and intertrochanter of the femur, and lumbar spine, was performed using dual-energy X-ray absorptiometry. The multivariable linear regression model for the association between dietary selenium intake and BMD and the generalized additive model (GAM) for the dose-response relationship were used.

Results: A total of 21,939 participants were included. The mean age was 40.68±22.42 years, and 51.28% were male. In the multivariable adjustment model, participants with the highest quintiles of dietary selenium intake (Q5) were associated with increased BMD levels in the total femur (β=0.014, 95% CI: 0.008–0.020, P<0.001), femur neck (β=0.010, 95% CI: 0.004–0.016, P=0.001), trochanter (β=0.011, 95% CI: 0.005–0.017, P<0.001), intertrochanter (β=0.017, 95% CI: 0.010–0.025, P<0.001), and lumbar spine (β=0.013, 95% CI: 0.005–0.020, P<0.001) compared with those in quintile 1 (Q1). The dose-response relationship showed an inverted U-shape relationship between dietary selenium intake and BMD levels (P for nonlinearity <0.05). Participants tended to have increased levels of BMD as the dietary selenium intake increased when dietary selenium was below the turning point, and then a negative relationship was observed when dietary intake was higher than the turning point.

Conclusions: Our study indicated that dietary selenium intake exhibited an inverted U-shape trend in relation to BMD levels, which demonstrates the need for selenium status in the body to be considered when discussing the role of dietary selenium intake in BMD. Future studies are needed to confirm these findings and explore the underlying biological mechanism.

Keywords: Dietary selenium intake; bone mineral density (BMD); nonlinear relationship; cross-sectional

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Introduction

Osteoporosis is a systemic bone disease that is common worldwide. Approximately 10.2 million people aged 50 years and over had osteoporosis in 2010 in the US, and the number is expected to reach 13.5 million by 2030 (1,2). Osteoporosis, characterized by reduced bone mass, low bone mineral density (BMD), and bone microstructure deterioration (3,4), increases the risk of all-cause mortality, including cardiovascular- and cancer-related mortality (5-7). The etiology of reduced bone mass and the development of osteoporosis is related to multiple factors, including genetic, environmental, and dietary factors (8,9). Furthermore, oxidative stress has been implicated as a causative factor for many disease states, including the diminished BMD in osteoporosis. The consumption of natural antioxidant-rich foods and isolated antioxidant supplementation may increase BMD and reduce the risk of brittleness-related fractures (10). Therefore, an understanding of the role of dietary antioxidant nutrients intake in increasing BMD has important implications for improving preventative measures that can combat this important contributor to morbidity and mortality worldwide.

The element selenium is an essential micronutrient that forms the so-called "selenoproteins" when incorporated into the polypeptide chain of proteins. Selenoproteins and selenium-dependent enzymes are involved in many crucial biological mechanisms, such as antioxidant and anti-inflammatory pathways (11,12), intracellular redox regulation (13), and thyroid hormone metabolism (14). A previous observational study demonstrated that the serum selenium concentration was positively associated with bone outcomes, including BMD and fracture risk (15). In a cross-sectional study, the relationship between serum selenium and the risk of osteoporosis-related fracture was nonlinear, but a strong positive correlation was evident between osteoporosis-related fracture risk and relatively high selenium exposure (16). At present, few studies have examined the effects of dietary selenium intake on bone health, and those that have are limited by small sample sizes.

One study suggested that antioxidant intake, including selenium, β-carotene, vitamin C, and vitamin E, was inversely associated with the risk of osteoporotic hip fracture in an older population of smokers (17). However, a prospective population-based cohort study indicated that sodium selenite supplementation did not affect bone turnover markers or physical performance in postmenopausal women with osteopenia (18).

The aim of present was to investigate the association between dietary selenium intake and BMD. Given that the site-discordance in BMD assessment is common and significantly affects patient categorization, we assessed the BMD level at multiple sites, including the femur, femur neck, trochanter and intertrochanter of the femur, and lumbar spine. Data on dietary intake was drawn from the cross-sectional National Health and Nutrition Examination Survey (NHANES). Furthermore, we examined the nonlinear dose-response association between dietary selenium intake and BMD. We present the following article in accordance with the SURGE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3441/rc).

Methods

Study population

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). We used data from the NHANES, which is a population-based cross-sectional survey designed to assess the health, nutritional status, and potential risk factors of the civilian, noninstitutionalized population of the US. The consecutive surveys are conducted by the NCHS of the Centers for Disease Control (CDC) via in-person interviews, physical examinations, and laboratory tests in a mobile examination center (MEC). Approximately 5,000 individuals at 15 geographic sites are selected by a multistage, stratified probability sampling design every 2 years. We extracted and aggregated data from 4 cycles of the NHANES [2005–2010, 2013–2014]. Participants with missing information on dietary selenium intake and BMD were excluded. Data on 21,939 participants were available for analysis of the total femur, femur neck, and trochanter and intertrochanter of the femur, and 18,116 participants were available for analysis of the lumbar spine. The detailed description of the NHANES was published elsewhere (6,19). All authors declared that all methods in this study were carried out in accordance with relevant guidelines and regulations.

Assessment of dietary selenium intake

Dietary selenium intake and other food components, including dietary fiber and calcium intake, were obtained from 24-hour dietary recall interviews, which were

conducted in the MEC. During the interview, participants were asked to recall the details of food and beverages consumed in the 24-hour period before the interview. Dietary intake data were collected using dietary data collection instrument of US Department of Agriculture (USDA) with the Automated Multiple Pass Method (AMPM) (http://www.ars.usda.gov/ba/bhnrc/fsrg). The AMPM was validated in the large studies and shown to be an effective method for collecting accurate nutrients intake of adults. For each participant, nutrient intake from each food or beverage was estimated. The present dietary intake data do not include nutrients obtained from dietary supplement intakes, antacids, or medications. The dietary selenium intake was calculated as microgram per day (μg/day).

BMD measurement

BMD measurement was performed using dual-energy X-ray absorptiometry (DXA) with Hologic QDR 4500A fan-beam densitometers (Hologic Inc., Bedford, MA, USA) (6), which is an internationally accepted standard-of-care screening tool used to assess fragility-fracture risk (20). The DXA examinations were administered by trained and certified radiology technologists. DXA scans were administered to eligible survey participants 8 years of age and older. Pregnant females, those with a self-reported history of radiographic contrast material in the past 7 days, and those who weighed over 300 pounds were ineligible for the DXA examination.

Other covariates

The covariates, including age (years), sex (male and female), race (non-Hispanic white, non-Hispanic black, Mexican American, or other race/ethnicity), education (under high school, high school, or above high school), and family income (under $20,000, $20,000–$55,000, or $55,000 and over), were obtained from in-person household interviews. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2), and was classified into underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥30 kg/m^2). Furthermore, leisure time physical activity [<500 metabolic equivalent (MET)/week, 500–999 MET/week, or ≥1,000 MET/week], smoking status (yes or no), alcohol use (yes or no), diabetes (yes or no), and hypertension (yes or no) were ascertained using questionnaires, which were self-reported by the participants.

Statistical analysis

Descriptive characteristics were summarized using means ± standard deviation (SD) for continuous variables and proportions for categorical variables. Data analyses accounted for the masked variance and used the recommended weighting methodology. Dietary selenium intake was divided into quintiles, and the differences in descriptive characteristic across quintiles were evaluated with analysis of variance (ANOVA) for continuous variables and chi-squared for categorical variables. We used multivariable linear regression models to assess the association between dietary selenium intake and BMD. Three models were used in the current analysis: model 1 was a crude model without adjustment for potential confounders; model 2 was adjusted for age and sex; and model 3 was further adjusted for race, education, family income, BMI, leisure time physical activity, smoking status, alcohol use, dietary fiber intake, calcium intake, diabetes, and hypertension. We also assessed the dose-response relationship between dietary selenium intake and BMD by using a generalized additive model (GAM). Moreover, to test the robustness of our findings, we used subgroup analyses by age (<50 *vs.* ≥50 years) and sex. All statistical analyses were performed using R software (version 3.5.3) and EmpowerStats (R) (www.empowerstats.com, X&Y solutions, Inc. Boston, MA, USA). Statistical significance was indicated by a two-sided P value <0.05.

Results

Characteristics of the participants included in the present study are shown in *Table 1*. Of the 21,939 participants, the mean age was 40.68±22.42 years, and 51.28% were male. Approximately 43% of participants were non-Hispanic white, and 44.54% of participants had an education level less than high school. Compared with participants in quintile 1 (Q1), those in higher quintiles (Q2–Q5) tended to be younger, male, non-Hispanic white, and have higher education, higher family income, more smoking and alcohol use, more leisure time physical activity, more dietary fiber and calcium intake, and a lower prevalence of diabetes and hypertension.

The unadjusted and multivariable adjusted associations between dietary selenium intake and BMD, including total femur, femur neck, trochanter, intertrochanter, and lumbar spine, are shown in *Table 2*. In the crude model, compared with the lowest quintiles of dietary selenium intake, higher dietary selenium intake was linked with increased BMD levels (all P trend <0.001). After adjustment

Table 1 Characteristics of the participants

Characteristics	Total population (n=21,939)	Dietary selenium intake (quintile)					
		Q1 (n=4,376)	Q2 (n=4,395)	Q3 (n=4,369)	Q4 (n=4,403)	Q5 (n=4,396)	P value
Age, years, mean ± SD	40.68±22.42	41.87±24.24	41.35±23.66	40.29±22.86	40.67±21.67	39.21±19.28	<0.001
Male, n (%)	11,251 (51.28)	1,509 (34.48)	1,802 (41.00)	2,141 (49.00)	2,523 (57.30)	3,276 (74.52)	<0.001
Race, n (%)							<0.001
Non-Hispanic white	9,510 (43.35)	1,782 (40.72)	1,916 (43.59)	1,864 (42.66)	2,005 (45.54)	1,943 (44.20)	
Black	4,684 (21.35)	1,088 (24.86)	945 (21.50)	916 (20.97)	857 (19.46)	878 (19.97)	
Mexican American	4,549 (20.73)	877 (20.04)	926 (21.07)	943 (21.58)	885 (20.10)	918 (20.88)	
Other Hispanic	1,920 (8.75)	398 (9.10)	371 (8.44)	391 (8.95)	382 (8.68)	378 (8.60)	
Other race/ethnicity	1,276 (5.82)	231 (5.28)	237 (5.39)	255 (5.84)	274 (6.22)	279 (6.35)	
Education, n (%)							<0.001
Under high school	9,764 (44.54)	2,212 (50.62)	2,049 (46.63)	1,978 (45.32)	1812 (41.19)	1,713 (38.99)	
High school	4,055 (18.50)	799 (18.28)	799 (18.18)	782 (17.92)	816 (18.55)	859 (19.55)	
Above high school	8,102 (36.96)	1,359 (31.10)	1546 (35.18)	1605 (36.77)	1,771 (40.26)	1,821 (41.45)	
Family income, n (%)							<0.001
Under $20,000	4,830 (22.83)	1,122 (26.71)	1,021 (24.00)	956 (22.71)	845 (19.87)	886 (20.89)	
$20,000–$55,000	8,239 (38.94)	1,706 (40.61)	1,676 (39.40)	1,664 (39.52)	1,631 (38.35)	1,562 (36.83)	
$55,000 and over	8,090 (38.23)	1,373 (32.68)	1,557 (36.60)	1,590 (37.77)	1,777 (41.78)	1,793 (42.28)	
Height, cm, mean ± SD	164.73±12.72	161.32±12.01	162.00±12.60	163.77±12.73	166.19±12.44	170.35±11.65	<0.001
Weight, kg, mean ± SD	73.41±21.62	70.08±20.60	70.51±21.40	72.20±21.67	75.17±21.64	79.04±21.47	<0.001
Body mass index, kg/m^2, mean ± SD	26.66±6.26	26.56±6.31	26.43±6.40	26.50±6.30	26.83±6.15	26.96±6.13	0.013
Smoking status, n (%)	7,532 (47.54)	1,406 (46.40)	1,433 (46.26)	1,399 (45.47)	1,605 (49.08)	1,689 (50.15)	<0.001
Alcohol use, n (%)	4,503 (20.53)	612 (13.99)	742 (16.88)	858 (19.64)	972 (22.08)	1,319 (30.00)	<0.001
Leisure time physical activity, MET/week, n (%)							0.045
<500	10,029 (54.68)	2,118 (59.16)	2,032 (57.29)	1,996 (55.49)	1,980 (53.35)	1,903 (48.73)	
500–999	2,251 (12.27)	395 (11.03)	463 (13.05)	439 (12.20)	474 (12.77)	480 (12.29)	
≥1,000	6,060 (33.04)	1,067 (29.80)	1,052 (29.66)	1,162 (32.30)	1,257 (33.87)	1,522 (38.98)	
Dietary fiber intake, g, mean ± SD	15.67±9.68	10.56±7.23	13.43±7.83	15.31±8.39	17.18±8.85	21.85±11.60	<0.001
Calcium intake, mg, mean ± SD	936.97±601.26	553.73±363.11	768.28±397.13	895.80±446.07	1,061.54±529.48	1,403.27±792.23	<0.001
Diabetes, n (%)	1,852 (8.59)	417 (9.70)	374 (8.67)	375 (8.75)	373 (8.63)	313 (7.23)	0.002
Hypertension, n (%)	5,733 (32.21)	1,264 (36.96)	1,193 (34.30)	1,118 (32.51)	1,134 (31.31)	1,024 (26.65)	<0.001
Bone mineral density, gm/cm^2, mean ± SD							
Total femur	0.95±0.17	0.91±0.17	0.93±0.17	0.94±0.17	0.97±0.17	1.00±0.17	<0.001
Femur neck	0.83±0.16	0.81±0.16	0.81±0.16	0.83±0.16	0.84±0.15	0.87±0.16	<0.001
Trochanter	0.72±0.14	0.70±0.14	0.70±0.14	0.72±0.14	0.74±0.14	0.76±0.14	<0.001
Intertrochanter	1.11±0.21	1.07±0.20	1.08±0.21	1.11±0.20	1.13±0.20	1.18±0.20	<0.001
Lumbar spine	0.97±0.19	0.95±0.19	0.95±0.20	0.96±0.19	0.98±0.19	1.01±0.17	<0.001

Q1, quintile 1; Q2–Q5, higher quintiles. SD, standard deviation; MET, metabolic equivalent.

Table 2 The association between dietary selenium intake and bone mineral density

Dietary selenium intake (quintile)	Model 1		Model 2		Model 3	
	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
Total femur, gm/cm^2						
Q1	Reference		Reference		Reference	
Q2	0.011 (0.004, 0.018)	0.002	0.005 (–0.002, 0.012)	0.150	0.005 (–0.001, 0.010)	0.091
Q3	0.028 (0.021, 0.035)	<0.001	0.015 (0.008, 0.021)	<0.001	0.007 (0.002, 0.013)	0.011
Q4	0.051 (0.044, 0.058)	<0.001	0.030 (0.023, 0.037)	<0.001	0.012 (0.006, 0.018)	<0.001
Q5	0.090 (0.083, 0.097)	<0.001	0.052 (0.045, 0.060)	<0.001	0.014 (0.008, 0.020)	<0.001
P trend	<0.001		<0.001		<0.001	
Femur neck, gm/cm^2						
Q1	Reference		Reference		Reference	
Q2	0.005 (–0.001, 0.012)	0.117	0.001 (–0.006, 0.007)	0.838	0.002 (–0.003, 0.007)	0.505
Q3	0.020 (0.013, 0.027)	<0.001	0.009 (0.003, 0.015)	0.006	0.005 (–0.001, 0.010)	0.078
Q4	0.035 (0.029, 0.042)	<0.001	0.020 (0.014, 0.027)	<0.001	0.008 (0.003, 0.014)	0.004
Q5	0.066 (0.060, 0.073)	<0.001	0.039 (0.032, 0.045)	<0.001	0.010 (0.004, 0.016)	0.001
P trend	<0.001		<0.001		<0.001	
Trochanter, gm/cm^2						
Q1	Reference		Reference		Reference	
Q2	0.009 (0.003, 0.015)	0.003	0.003 (–0.002, 0.009)	0.228	0.003 (–0.002, 0.008)	0.189
Q3	0.021 (0.015, 0.026)	<0.001	0.009 (0.003, 0.014)	0.002	0.003 (–0.001, 0.008)	0.172
Q4	0.040 (0.034, 0.045)	<0.001	0.021 (0.016, 0.027)	<0.001	0.009 (0.004, 0.014)	<0.001
Q5	0.069 (0.063, 0.075)	<0.001	0.037 (0.031, 0.042)	<0.001	0.011 (0.005, 0.017)	<0.001
P trend	<0.001		<0.001		<0.001	
Intertrochanter, gm/cm^2						
Q1	Reference		Reference		Reference	
Q2	0.013 (0.005, 0.022)	0.002	0.007 (–0.001, 0.015)	0.099	0.006 (0.000, 0.013)	0.048
Q3	0.034 (0.025, 0.042)	<0.001	0.020 (0.011, 0.028)	<0.001	0.011 (0.004, 0.017)	0.001
Q4	0.060 (0.052, 0.069)	<0.001	0.037 (0.029, 0.046)	<0.001	0.015 (0.008, 0.022)	<0.001
Q5	0.106 (0.097, 0.114)	<0.001	0.066 (0.057, 0.074)	<0.001	0.017 (0.010, 0.025)	<0.001
P trend	<0.001		<0.001		<0.001	
Lumbar spine, gm/cm^2						
Q1	Reference		Reference		Reference	
Q2	–0.001 (–0.009, 0.008)	0.892	–0.001 (–0.009, 0.008)	0.866	–0.001 (–0.008, 0.005)	0.654
Q3	0.008 (–0.000, 0.017)	0.061	0.010 (0.002, 0.019)	0.017	0.003 (–0.003, 0.010)	0.329
Q4	0.032 (0.023, 0.041)	<0.001	0.031 (0.023, 0.039)	<0.001	0.011 (0.004, 0.018)	0.001
Q5	0.057 (0.048, 0.066)	<0.001	0.057 (0.048, 0.065)	<0.001	0.013 (0.005, 0.020)	<0.001
P trend	<0.001		<0.001		<0.001	

Model 1: crude model; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex (male and female), race (non-Hispanic white, non-Hispanic black, Mexican American, other race/ethnicity, or missing), education (under high school, high school, above high school, or missing), family income (under $20,000, $20,000–$55,000, $55,000 and over, or missing), body mass index (underweight, normal weight, overweight, obese, or missing), leisure time physical activity (<500 MET/week, 500–999 MET/week, ≥1,000 MET/week, or missing), smoking status (yes, no, or missing), alcohol use (yes, no, or missing), dietary fiber intake, calcium intake, diabetes (yes, no, or missing), and hypertension (yes, no, or missing). Q1, quintile 1; Q2–Q5, higher quintiles. MET, metabolic equivalent.

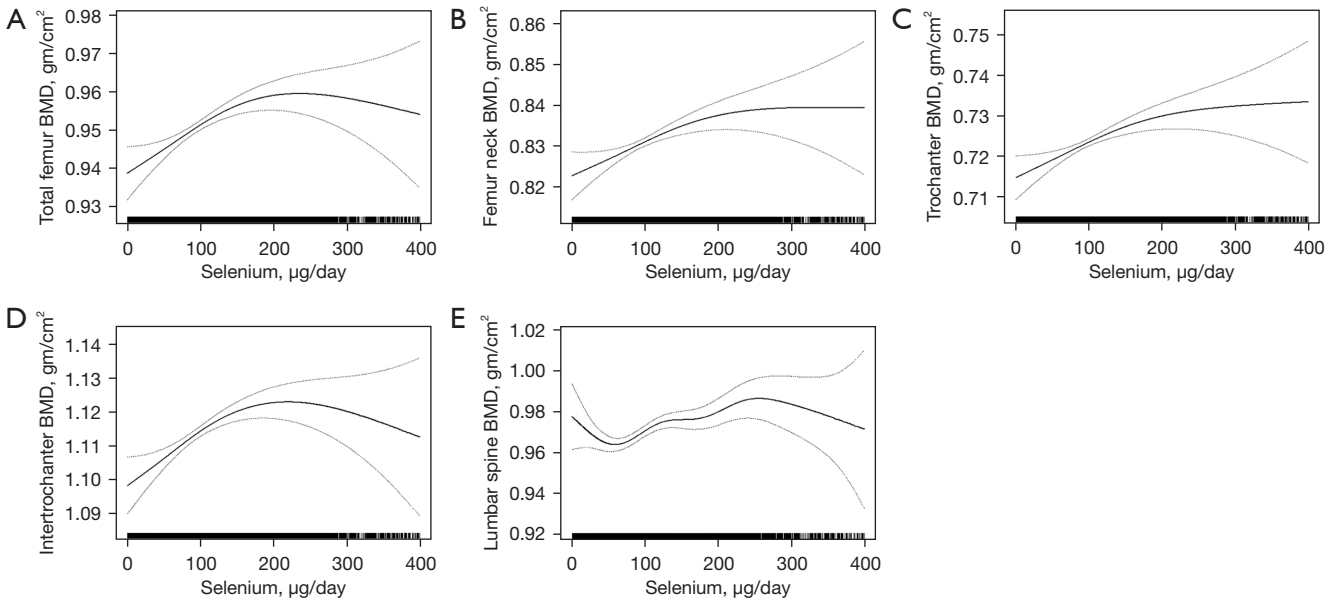

Figure 1 The dose-response relationship between dietary selenium intake and bone mineral density. (A) Total femur; (B) femur neck; (C) trochanter; (D) intertrochanter; (E) lumbar spine. BMD, bone mineral density.

for potential confounders, the results were also consistent. In the multivariable model, participants with the highest quintiles of dietary selenium intake (Q5) were associated with increased BMD levels in the total femur (β=0.014, 95% CI: 0.008–0.020, P<0.001), femur neck (β=0.010, 95% CI: 0.004–0.016, P=0.001), trochanter (β=0.011, 95% CI: 0.005–0.017, P<0.001), intertrochanter (β=0.017, 95% CI: 0.010–0.025, P<0.001), and lumbar spine (β=0.013, 95% CI: 0.005–0.020, P<0.001) compared with those in quintiles 1 (Q1).

We further used the GAM to examine the dose-response association, and found an inverted U-shape association between dietary selenium intake and BMD levels (*Figure 1*). Overall, participants tended to have increased levels of BMD as the dietary selenium intake increased when dietary selenium intake was below the turning point, and then the BMD decreased as the dietary selenium intake increased when dietary selenium intake was higher than the turning point. Furthermore, we used a log likelihood ratio test which showed significant differences between the linear model and segmented regression model, indicating that the associations between dietary selenium intake and BMD levels of the total femur (P<0.001), femur neck (P=0.003), trochanter (P=0.005), intertrochanter (P<0.001), and lumbar spine (P=0.004) were nonlinear.

In the subgroups stratified by age, the highest quintiles of dietary selenium intake were positively associated with increased BMD levels in the total femur, femur neck, trochanter, intertrochanter, and lumbar spine (*Table 3*). In contrast, no statistical associations were observed between the highest quintiles of dietary selenium intake and BMD levels in females.

Discussion

We analyzed data from a large-scale nationally representative population-based cross-sectional study (NHANES) and determined that higher dietary selenium intake was associated with increased BMD in the femur, femur neck, trochanter, intertrochanter, and lumbar spine, and the effect remained consistent across various age groups and genders. Furthermore, the results from the GAM suggested a nonlinear inverted U-shape association between dietary selenium intake and BMD.

Severe selenium deficiency is associated with Keshan disease, an endemic osteoarticular cardiomyopathy that is characterized by the selective necrosis of articular and growth plate chondrocytes (21). Bone has the second highest proportion of selenium (16%) in the body, only exceeded by skeletal muscles (27.5%) (22). Few studies have examined the association between dietary selenium intake and bone health, leading to inconsistent epidemiological results. One study demonstrated that dietary selenium supplementation did not

Table 3 The association between dietary selenium intake and bone mineral density by different age and sex

Dietary selenium intake (quintile)	Age <50		Age ≥50		Male		Female	
	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
Total femur, gm/cm^2								
Q1	Reference		Reference		Reference		Reference	
Q2	−0.002 (−0.008, 0.005)	0.641	0.013 (0.004, 0.022)	0.003	0.006 (−0.003, 0.015)	0.186	0.002 (−0.005, 0.008)	0.620
Q3	0.004 (−0.003, 0.011)	0.221	0.013 (0.004, 0.022)	0.005	0.005 (−0.004, 0.014)	0.260	0.006 (−0.001, 0.013)	0.082
Q4	0.010 (0.003, 0.018)	0.005	0.017 (0.008, 0.027)	<0.001	0.010 (0.001, 0.019)	0.029	0.012 (0.005, 0.020)	0.001
Q5	0.015 (0.007, 0.022)	<0.001	0.020 (0.009, 0.030)	<0.001	0.016 (0.007, 0.025)	<0.001	0.004 (−0.005, 0.013)	0.356
P trend	<0.001		<0.001		<0.001		0.012	
Femur neck, gm/cm^2								
Q1	Reference		Reference		Reference		Reference	
Q2	0.000 (−0.007, 0.007)	0.959	0.006 (−0.002, 0.014)	0.156	0.002 (−0.006, 0.011)	0.599	0.000 (−0.006, 0.006)	0.960
Q3	0.005 (−0.002, 0.012)	0.158	0.009 (0.001, 0.018)	0.031	0.002 (−0.006, 0.010)	0.646	0.006 (−0.001, 0.012)	0.095
Q4	0.010 (0.002, 0.017)	0.009	0.013 (0.005, 0.022)	0.003	0.005 (−0.003, 0.014)	0.205	0.010 (0.003, 0.017)	0.005
Q5	0.012 (0.004, 0.019)	0.003	0.019 (0.009, 0.029)	<0.001	0.012 (0.004, 0.021)	0.005	0.001 (−0.008, 0.009)	0.869
P trend	<0.001		<0.001		0.002		0.055	
Trochanter, gm/cm^2								
Q1	Reference		Reference		Reference		Reference	
Q2	−0.002 (−0.008, 0.004)	0.484	0.010 (0.002, 0.017)	0.014	0.005 (−0.003, 0.013)	0.221	−0.000 (−0.006, 0.006)	0.976
Q3	0.001 (−0.006, 0.007)	0.848	0.008 (−0.000, 0.016)	0.059	0.002 (−0.006, 0.010)	0.610	0.002 (−0.004, 0.008)	0.559
Q4	0.007 (0.001, 0.013)	0.032	0.012 (0.004, 0.020)	0.004	0.007 (−0.001, 0.015)	0.078	0.008 (0.002, 0.015)	0.013
Q5	0.011 (0.004, 0.017)	0.003	0.015 (0.005, 0.024)	0.002	0.013 (0.004, 0.021)	0.003	0.004 (−0.004, 0.012)	0.344
P trend	<0.001		0.003		0.002		0.034	
Intertrochanter, gm/cm^2								
Q1	Reference		Reference		Reference		Reference	
Q2	−0.002 (−0.010, 0.006)	0.678	0.017 (0.007, 0.028)	0.001	0.007 (−0.003, 0.018)	0.163	0.004 (−0.004, 0.011)	0.372
Q3	0.007 (−0.001, 0.015)	0.092	0.017 (0.007, 0.028)	0.002	0.008 (−0.003, 0.018)	0.144	0.010 (0.001, 0.018)	0.024
Q4	0.012 (0.004, 0.021)	0.004	0.021 (0.010, 0.033)	<0.001	0.012 (0.001, 0.022)	0.030	0.016 (0.007, 0.025)	<0.001
Q5	0.018 (0.009, 0.027)	<0.001	0.022 (0.010, 0.035)	<0.001	0.018 (0.007, 0.029)	<0.001	0.006 (−0.005, 0.017)	0.251
P trend	<0.001		<0.001		<0.001		0.006	
Lumbar spine, gm/cm^2								
Q1	Reference		Reference		Reference		Reference	
Q2	−0.006 (−0.014, 0.001)	0.072	0.005 (−0.008, 0.017)	0.469	−0.001 (−0.011, 0.010)	0.887	−0.004 (−0.012, 0.003)	0.270
Q3	0.002 (−0.006, 0.009)	0.648	0.004 (−0.009, 0.017)	0.555	−0.000 (−0.010, 0.010)	0.960	0.003 (−0.006, 0.011)	0.502
Q4	0.013 (0.005, 0.020)	0.001	0.006 (−0.007, 0.020)	0.370	0.006 (−0.004, 0.016)	0.232	0.014 (0.005, 0.023)	0.002
Q5	0.017 (0.009, 0.025)	<0.001	0.003 (−0.012, 0.018)	0.705	0.016 (0.005, 0.026)	0.003	−0.002 (−0.013, 0.009)	0.759
P trend	<0.001		0.642		<0.001		0.055	

Model 1: crude model; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex (male and female), race (non-Hispanic white, non-Hispanic black, Mexican American, other race/ethnicity, or missing), education (under high school, high school, above high school, or missing), family income (under $20,000, $20,000–$55,000, $55,000 and over, or missing), body mass index (underweight, normal weight, overweight, obese, or missing), leisure time physical activity (<500 MET/week, 500–999 MET/week, ≥1,000 MET/week, or missing), smoking status (yes, no, or missing), alcohol use (yes, no, or missing), dietary fiber intake, calcium intake, diabetes (yes, no, or missing), and hypertension (yes, no, or missing). Q1, quintile 1; Q2–Q5, higher quintiles. MET, metabolic equivalent.

attenuate mammary tumorigenesis-mediated bone loss in a male mouse breast cancer model (23). A recent randomized double-blinded controlled study by Walsh *et al.* reported that 200 μg/day selenium supplementation did not affect the musculoskeletal health of postmenopausal women (24). However, in the present study, a higher dietary selenium intake did result in increased BMD. In line with our findings, a cross-sectional study that included 6,267 participants demonstrated that compared with those in the lowest quartile of dietary selenium intake, those belonging to the fourth quartile exhibited a lower odds ratio for osteoporosis (OR: 0.47, 95% CI: 0.31–0.73) (25). Zhang *et al.* observed that selenium intake was negatively associated with the risk of osteoporotic hip fracture (17).

The biological mechanisms responsible for the effects of selenium intake on BMD are uncertain. A previous study demonstrated that changes in the redox state can alter the bone remodeling process, which allows continuous bone regeneration through the coordination of the 3 major types of bone cells: osteoclasts, osteoblasts, and osteocytes (26). Changes in reactive oxygen species (ROS) and/or antioxidant systems may be involved in the pathogenesis of bone loss. Osteoblast and osteocyte apoptosis induced by ROS leads to osteoclast formation and inhibits mineralization and osteogenesis. Excessive osteocyte apoptosis is associated with oxidative stress that leads to imbalanced osteoclast formation, which results in increased bone remodeling and bone loss (26-28). Moreover, selenium plays a crucial role in antioxidant, immunological, and anti-inflammatory processes. The physiological function of the essential micronutrient selenium is mainly mediated by selenoproteins (29), which have antioxidant activities and are known to maintain the redox cell balance, protect against oxidative stress caused by ROS, and regulate inflammation and osteocyte proliferation and differentiation (30). Furthermore, it has been reported that interleukin-6 (IL-6) and other cytokines play a crucial role in the pathogenesis of osteoporosis (31). Therefore, the anti-inflammatory effect of selenium may be partly mediated by inhibiting the activity of IL-6 and cytokines (25,32). Another potential mechanism linking selenium to bone health is the relationship between selenium-dependent glutathione peroxidase and thyroid protection (33). Therefore, selenium deficiency may increase the level of thyroid hormone in the blood, leading to accelerated bone loss and osteoporosis (34).

Although limited data confirm the effects of dietary selenium supplementation on bone health, the accumulated evidence indicates a positive association between circulating selenium concentrations and bone outcomes. A population-based cohort study conducted in 5 European cities demonstrated that higher selenium levels were associated with increased hip BMD and decreased bone formation at the beginning of the research (15). Other studies have indicated that selenium deficiency can hinder bone growth and alter bone metabolism (35,36). In a survey conducted in the US, increased serum selenium concentrations were associated with increased femur BMD, decreased Fracture Risk Assessment Tool (FRAX) scores, and a reduced history of bone fractures (37). A study that used plasma selenium and selenoprotein P as biomarkers demonstrated that an increase in selenium content was associated with an increase in BMD in the lumbar spine and hip in European postmenopausal women (38). In addition, low hair selenium levels have been reported to be associated with low lumbar and femoral BMD values in Korean adults (39). The finding of a positive correlation between dietary selenium intake and blood selenium concentration (40,41) suggests that selenium supplementation may positively influence bone health in selenium-deficient patients.

Some observational studies have reported a U-shape relationship between serum selenium and the risk of diabetes, coronary heart disease, anemia, and all-cause mortality (40,42-44). Data from the NHANES III indicate an inverse association between serum selenium and all-cause mortality at low selenium levels (<130 ng/mL) and a modest increase in mortality at high selenium levels (>150 ng/mL) (45). Similar to the findings of these studies, the results of our study indicate a positive relationship between dietary selenium intake and BMD when dietary selenium intake is below a certain threshold, and a negative relationship when dietary selenium intake is higher than that threshold. This may be because selenium is an essential element with a narrow safety margin, and higher concentrations often lead to toxicity (42). Furthermore, the regulation of selenium levels in the body mainly depends on its excretion rather than absorption. When dietary selenium intake is high enough to optimize the levels of selenium protein, any further intake is completely offset by excreta, allowing for only a slight increase in systemic selenium (46).

The present study has several strengths. To our knowledge, this is the first study to assess the nonlinear relationship between dietary selenium intake and BMD in the femur, femur neck, trochanter, intertrochanter, and lumbar spine. Our study was based on a large nationally representative survey, and BMD was measured in a reliable

independent lab using established methods. Moreover, we adjusted numerous potentially confounding factors, including socioeconomic, lifestyle, and nutrient intake factors. However, our study also has some limitations. First, as a cross-sectional study, inferring a causal association between dietary selenium intake and BMD is challenging. Second, the dietary intake data of NHANES were obtained from 24-hour dietary recall interviews, and could be susceptible to recall bias. Third, because of the limitations of the original data, we did not assess the association between dietary selenium intake and the risk of osteoporosis, and association between serum selenium and BMD level. Future large-scale, prospective studies are required to confirm the findings of this study.

Conclusions

In summary, our study suggests that higher dietary selenium intake is associated with increased BMD in the femur, femur neck, trochanter, intertrochanter, and lumbar spine. Furthermore, this study identified an inverted U-shape relationship between dietary selenium intake and BMD. Future large-scale, prospective studies are required to confirm these findings.

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Footnote

Reporting Checklist: The authors have completed the SURGE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3441/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3441/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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