

Association Between Bone Mineral Density And Serum Creatinine In People < 46 Years Old

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Research Article

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Abstract

Purpose: To research the relationship between serum creatinine and lumbar bone mineral density in people aged <46 years.

Methods: A total of 10,968 subjects from the American Nhanes database were included in this cross-sectional study, including 5,744 males (mean age 26.2 years) and 5224 females (mean age 26.7 years). The exposure factor is the serum creatinine value, and the outcome indicator is the lumbar bone mineral density. This study mainly used multivariate linear regression analysis to test the relationship between lumbar bone mineral density and serum creatinine.

Results: In the multivariate linear regression analysis, serum creatinine was positively correlated with lumbar bone mineral density ($\beta = 0.122$, 95%CI: 0.047-0.198), but in the subgroup analysis stratified by sex, this positive correlation only exists in the female population ($B = 0.186$, 95%CI: 0.070-0.301).

Conclusions: Our study found that in women aged <46 years with normal renal function, there is a positive correlation between serum creatinine and lumbar BMD. And in those people, the determination of serum creatinine can provide a sensitive biomarker for the early identification and treatment of Osteopenia or osteoporosis.

Introduction

Osteoporosis is the most common bone disease, characterized by low bone mineral density (BMD) and microstructural degradation [1, 2]. It increases the risk of fractures caused by less or minor trauma[3]. Osteoporosis can occur at any race, any age, and between men and women. Although the diagnosis and risk factors of osteoporosis and osteoporosis-related fractures and the treatments that can be used in postmenopausal women have been extensively studied, and now it has been clearly defined, Little is known about the risk factors for osteoporosis in premenopausal women and young men. In most young people, lower bone mineral density is due to lower peak bone mass and/or secondary causes, such as underlying disease or medication[4, 5]. The risk factors of low BMD in premenopausal females, including low body weight, amenorrhea, lack of exercise, smoking, and a daily diet low in calcium and vitamin D [6]. Since bone mass reaches its peak at 30 years of age, and 90% of bone development is completed at 18 years of age [7], the young period of whole life plays an important role in bone health and the prevention of later fracture. However, Only a few studies have evaluated healthy young people in the incidence of low bone mineral density.

More and more evidence supports the interrelationship between bones and muscles because they share common genetic, lifestyle, nutrition, and hormonal determinants[8]. The interaction between muscles and bones affects bone strength, and it has been previously shown that bones function as musculoskeletal units and adapt to the mechanical loads imposed by skeletal muscles[9, 10]. Serum creatinine main metabolite of creatine phosphate is present in skeletal muscle. Because of the same rate of decomposition of creatinine and creatinine skeletal muscle mass units, the stability of plasma creatinine

concentration can directly reflect the skeletal muscle mass[11]. From these research results and considering the skeletal muscle relationship, we speculate that Serum creatinine has a positive correlation with bone mineral density, especially in people with normal renal function. However, few studies have reported the relationship between bone mineral density and serum creatinine. Therefore, the purpose of this research is to investigate the relationship between serum creatinine and bone mineral density in normal renal function people, using the data from the NHANES database in the United States. We hypothesized that Serum creatinine is positively correlated with bone mineral density. Serum creatinine can provide information about individual bone and muscle health of people with normal renal function.

Materials And Methods

Ethics statement: This study was approved by the ethics review committee of the National Center for Health Statistics, and each participant's written consent was obtained. **Research population:** The NHANES is a representative survey of the United States (US) national population, using a complex, multi-stage, probability sampling design to provide a large amount of information about the nutrition and health of the general population in the United States. Our analysis is based on 2011–2018 data, which represent the four cycles of the NHANES database. After the exclusion of people with missing Serum creatinine data, lumbar BMD data, and Renal insufficiency, a total of 10968 people < 46 years old were included in our analysis (Fig. 1).

Variables: The exposure variable in this study is serum creatinine. The outcome variable is the BMD of the lumbar spine, measured by a dual-energy X-ray bone densitometer (DXA). The following categorical variables were included as covariates in our analysis: gender, race, education level, drinking, smoking behavior, physical activity. The continuous covariates included in our study were age, poverty to income ratio, body mass index (BMI), serum alkaline phosphatase, blood urea nitrogen (BUN), Dietary calcium, and vitamin D intake, Serum total calcium, serum phosphorus, Serum glucose. The detailed information of serum creatinine, lumbar spine BMD, and covariates are publicly available on the Nhanes database website(<http://www.cdc.gov/nchs/nhanes/>).

Statistical analysis: We performed a weighted and variance estimation analysis to explain the significant variance in our dataset. The association between serum creatinine and lumbar spine BMD was assessed by using a weighted multiple linear regression model. We used a weighted linear regression model for continuous variables or a weighted χ^2 test for categorical variables to calculate the difference between groups. Furthermore, The nonlinear relationship between serum creatinine and lumbar spine BMD was resolved by the use of smooth curve fitting. For missing data, we used multiple imputations, based on 5 replications and a chained equation approach method in the R MI procedure, for data filling. All analyses were conducted by using the R package and EmpowerStats, and a P-value of < 0.05 was considered statistically significant.

Result

There were 10968 people aged < 46 years included in our study, and the weighted characteristics of the participants were sub-categorized based on the quartile of serum creatinine (Q1: 0.25–0.64 mg/dL; Q2: 0.65-0.77mg/dL; Q3: 0.78–0.91 mg/dL; and Q4: 0.92–6.61 mg/dL), as shown in Table 1. The differences in baseline characteristics between the different gender have statistical significance. Compared to the female, the male participants were more likely to be a smoker, heavy worker, and have higher values of BUN, Dietary Calcium, Dietary Calcium, Alkaline phosphatase (ALP), Income to poverty ratio, Total Calcium, serum Creatinine, serum Glucose, serum Phosphorus, and lower values of Age, BMI, lumbar BMD.

Table 1. Characteristics of the study population based on gender

Gender	Male	Female	P-Value*
n	5744	5224	
Age	26.2 ± 10.1	26.7 ± 10.3	0.011
Income to poverty ratio	2.3 ± 1.6	2.2 ± 1.6	<0.001
BMI(Kg/m ²)	26.9 ± 6.7	27.5 ± 7.6	0.059
ALP(IU/L)	105.1 ± 82.9	75.3 ± 42.1	<0.001
Dietary Vitamin D(mcg/day)	5.3 ± 6.3	3.9 ± 4.8	<0.001
Dietary Calcium (mg/day)	1117.6 ± 712.9	849.7 ± 498.1	<0.001
BUN(mg/dl)	12.6 ± 3.8	10.7 ± 3.4	<0.001
Total Calcium (mg/dL)	9.5 ± 0.3	9.4 ± 0.3	<0.001
Creatinine (mg/dL)	0.9 ± 0.2	0.7 ± 0.1	<0.001
Creatinine categories			<0.001
Q1(0.25-0.64 mg/dL)	547 (9.5%)	2036 (39.0%)	
Q2(0.65-0.77mg/dL)	890 (15.5%)	1931 (37.0%)	
Q3(0.78-0.91 mg/dL)	1730 (30.1%)	990 (19.0%)	
Q4(0.92-6.61 mg/dL)	2577 (44.9%)	267 (5.1%)	
Glucose serum (mg/dL)	93.6 ± 25.2	91.6 ± 24.0	<0.001
Cholesterol serum (mg/dL)	176.2 ± 39.8	175.0 ± 35.4	0.934
Phosphorus (mg/dL)	4.0 ± 0.7	3.9 ± 0.6	<0.001
Race			0.012
Mexican American	984 (17.1%)	942 (18.0%)	
Other Hispanic	542 (9.4%)	571 (10.9%)	
Non-Hispanic White	1882 (32.8%)	1614 (30.9%)	
Non-Hispanic Black	1246 (21.7%)	1168 (22.4%)	
Other Race	1090 (19.0%)	929 (17.8%)	
Education level			<0.001
< 9th grade	188 (5.1%)	167 (4.9%)	
9-11th grade	500 (13.6%)	342 (10.1%)	
High school graduate	904 (24.6%)	607 (17.9%)	

Some college or AA degree	1140 (31.0%)	1284 (37.8%)	
College graduate or above	945 (25.7%)	997 (29.3%)	
Alcohol consumption			0.235
Yes	719 (89.2%)	651 (87.3%)	
No	87 (10.8%)	95 (12.7%)	
Smoked at least 100 cigarettes in life			<0.001
Yes	1646 (40.9%)	983 (26.5%)	
No	2378 (59.1%)	2731 (73.5%)	
Vigorous work activity			<0.001
Yes	1420 (28.3%)	576 (12.6%)	
No	3600 (71.7%)	3998 (87.4%)	
Lumbar BMD(g/cm ²)	1.007 ± 0.165	1.039 ± 0.137	<0.001

Mean ± SD for continuous variables, (%) for categorical variables. Abbreviation: bone mineral density (BMD), Body Mass Index (BMI), Alkaline phosphatase (ALP), blood urea nitrogen (BUN).

From Table 2, we can know the results of the multivariate regression analyses. In model 1, Serum Creatinine was positively correlated to lumbar BMD ($\beta = 0.200$, 95%CI: 0.187–0.214 $P < 0.00001$). This positive correlation between the two still exists ($\beta = 0.254$, 95%CI: 0.238–0.270, $P < 0.00001$) in the model 2 and model 3 ($\beta = 0.122$, 95%CI: 0.047–0.198 $P = 0.00161$). When we changed the serum creatinine from continuous variable to categorical variable, we can observe that the bone mineral density of the highest group increased by 0.051g/cm² compared to the lowest group.

Table 2
The association between Serum Creatinine and lumbar bone mineral density

Exposure	Model 1	Model 2	Model 3
	β (95% CI) P value	β (95% CI) P value	β (95% CI) P value
Creatinine (mg/dL)	0.200 (0.187, 0.214) < 0.00001	0.254 (0.238, 0.270) < 0.00001	0.122 (0.047, 0.198) 0.00161
Creatinine categories			
Q1(0.25–0.64 mg/dL)	Reference	Reference	Reference
Q2(0.65-0.77mg/dL)	0.062 (0.054, 0.070) < 0.00001	0.061 (0.053, 0.069) < 0.00001	0.018 (-0.016, 0.052) 0.31120
Q3(0.78–0.91 mg/dL)	0.080 (0.072, 0.088) < 0.00001	0.103 (0.095, 0.111) < 0.00001	0.012 (-0.025, 0.050) 0.51474
Q4(0.92–6.61 mg/dL)	0.112 (0.105, 0.120) < 0.00001	0.149 (0.140, 0.158) < 0.00001	0.051 (0.009, 0.093) 0.01758
Subgroup analysis stratified by gender			
Male	0.346 (0.326, 0.365) < 0.00001	0.286 (0.264, 0.307) < 0.00001	0.059 (-0.043, 0.162) 0.25788
Female	0.262 (0.237, 0.287) < 0.00001	0.186 (0.159, 0.212) < 0.00001	0.186 (0.070, 0.301) 0.00176
Model 1: no covariates were adjusted. Model 2: age, gender, and race were adjusted. Model 3: age, gender, race, BMI, physical activity, smoking behavior, alcohol consumption, BUN, serum phosphorus, serum calcium, serum Glucose, ALP, Income to poverty ratio, Dietary Vitamin D, and Dietary Calcium use were adjusted. In the subgroup analysis stratified by gender, the model is not adjusted for gender.			

According to the subgroup analysis based on gender, Presented in Table 2, the positive correlation between Serum Creatinine and lumbar BMD still exists in the female population ($\beta = 0.186$, 95%CI: 0.070–0.301, $P = 0.00176$), but not in male. The smooth curve fitting diagram between serum creatinine and lumbar bone mineral density is presented in Fig. 2–3.

Because there are some missing data from the participants, if participants with missing data are excluded from analysis, it may lead to selection bias and ultimately affect the results of statistical analysis. To maximize statistical power and minimize bias that might occur if participants with missing data were excluded from analysis, we used multiple imputation methods to supplement the missing data, and finally got five sets of data. We carried out multiple regression analyses on the five sets of data and reached five conclusions. We integrated the five conclusions and got the result that the lumbar BMD has a positive correlation with Serum Creatinine ($\beta = 0.154$, 95%CI: 0.136–0.170, $P < 0.00001$).

Discussion

This research is a cross-sectional study based on the National Health and Nutrition Examination Survey database in the United States. The result of the present study indicated that among people younger than 46 years old with normal renal function, people with low creatinine are at higher risk of low bone mineral density. In the subgroup analysis, the conclusions also apply to the female population. But in the male population, the correlation between serum creatinine and lumbar bone mineral density is not significant.

As we all know, muscle plays a vital role in physiology and metabolism. The theory that muscle contractions play an important role in bone strength and mass was supported by the correlation between grip strength and bone area, bone mineral content, and bone mineral density [12, 13]. Furthermore, some researchers believe that skeletal muscle mass has a positive relationship with bone mineral content and bone mineral density in the Mediterranean Intensive Oxidant Study [14–16]. Some hypotheses have also been proposed to explain the relationship between skeletal muscle mass and bone density. First, Skeletal muscle that communicating with other organs by secreting large amounts of protein and RNA has recently been considered an endocrine organ [17]. The bioactive molecules produced by muscles can promote the homeostasis of bone[18]. It is well known that various muscle-derived muscle factors and bone-derived bone factors can affect each other's tissues in a paracrine manner[19]. These findings indicate that skeletal muscle not only plays its classic musculoskeletal role but also interacts with bones through local and humoral signaling pathways. In addition, Muscle contraction causes tension in the bone, which in turn activates bone remodeling through bone cell mechanoreceptors. The contraction of skeletal muscles and the resulting mechanical forces on the bones are essential for modeling and remodeling. They can all increase bone strength and quality[20]. So, it is clear that maintaining skeletal muscle mass can effectively prevent the occurrence of osteoporosis.

Serum creatinine is a product of human muscle metabolism. In muscles, creatine slowly forms creatinine through an irreversible non-enzymatic dehydration reaction, which is then released into the blood and excreted in the urine. Therefore, serum creatinine is closely related to the total amount of muscle in the body.

Some studies have confirmed the relationship between serum creatinine and lean body mass[16, 21, 22], they found that In people with normal renal function, serum creatinine values are positively correlated with skeletal muscle mass.

Therefore, we believed that serum creatinine, a stable marker of skeletal muscle quality[23], is related to bone health, especially bone mineral density. So, we conducted this study to confirm the relationship between serum creatinine and bone mineral density in people with normal renal function. And eventually, as we hypothesized, this study confirmed that in people with normal renal function, the value of serum creatinine was positively correlated with bone mineral density. When we conducted a subgroup analysis of the participants by gender, we found that the positive correlation between serum creatinine and bone mineral density only exists in the female population. But the relationship between the two in the male population was not statistically significant.

However, this article still had some limitations. Most importantly, The design of the cross-sectional study limited the inference of the causal relationship between serum creatinine and lumbar bone mineral density. Therefore, further basic mechanism research and large-sample prospective studies are needed to determine the exact mechanism of the association between serum creatinine and lumbar bone mineral density. Secondly, there are still some unknown confounding factors that not be adjusted, which may lead to bias in the article

Conclusions

Our study confirmed that in women aged < 46 years with normal renal function, there is a positive correlation between serum creatinine and lumbar bone mineral density. And in those people, the measurement of serum creatinine can provide a responsive biomarker for the early identification and treatment of osteoporosis.

Abbreviations

BMD: Bone Mineral Density

NHANES: National Health and Nutrition Examination Survey

DXA: Dual-energy X-ray

BMI: Body Mass Index

BUN: Blood Urea Nitrogen

ALP: Alkaline phosphatase

Declarations

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Ethics approval and consent to participate—This study was approved by the ethics review committee of the National Center for Health Statistics, and each participant's written consent was obtained.

Consent for publication—All authors agree the publication of this paper.

Availability of data and materials: All data in this study comes from the Nhanes database, which is true and valid.

Competing interests: Yanru Guo and Xianyang Zhu declare that they have no conflict of interest.

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Authors' contributions: Both authors participated in the design of the research and data collection, among which Zhu Xianyang also participated in the analysis and calculation of the data and the writing of the article

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Figures

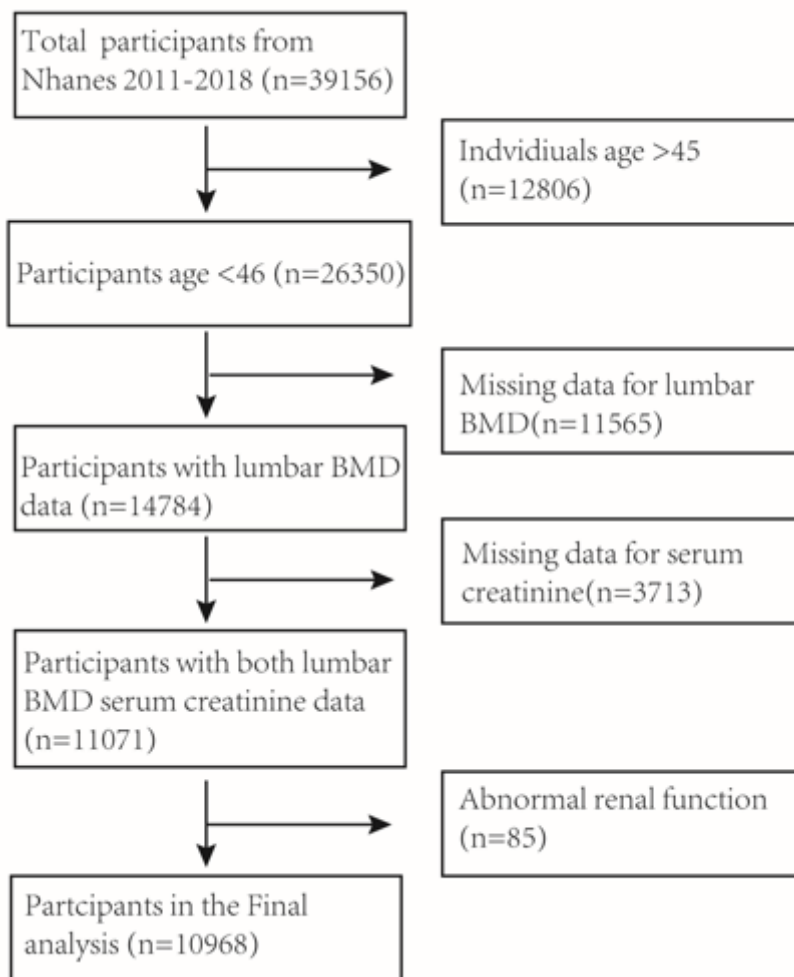


Figure 1

Flow chart of participants selected from the NHANES 2011–2018.

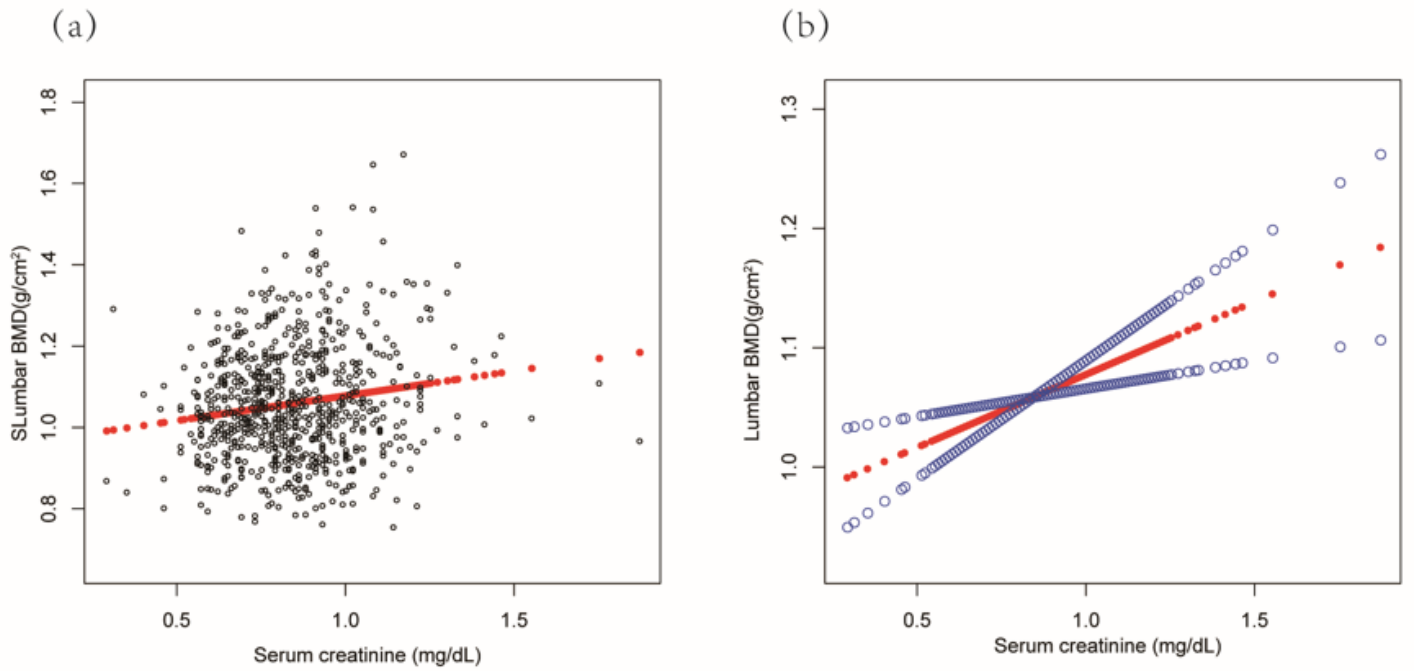


Figure 2

The association between serum creatinine and lumbar bone mineral density. (a) Each black point represents a sample. (b) The solid red line represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit.

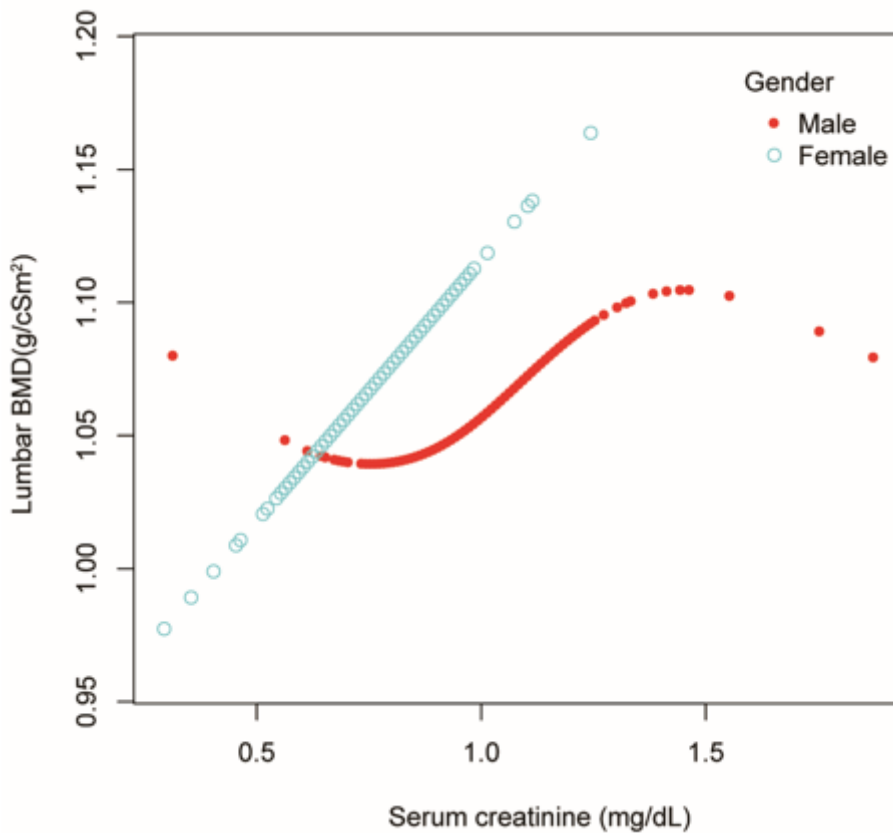


Figure 3

The association between serum creatinine and lumbar bone mineral density in different genders.