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The Relationship of Pulse Pressure and Bone Mineral Density in Adult USA Population: Analysis of the National Health and Nutritional Examination Survey

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Abstract

Background/Purpose: Accumulating evidence indicates a relationship between Cardiovascular Disease (CVD) and osteoporosis. Hypertension, a known risk factor for CVD is also associated with low Bone Mineral Density (BMD). We hypothesize that Pulse Pressure (PP); a CVD risk factor is associated with BMD.

Methods: Data from two consecutive cycles of National Health and Nutritional Examination Survey (NHANES) from 2009-2010 and 2011-2012. Point estimates of demographic variables were calculated using descriptive methods. Study participants were divided into 4 groups based on quartile distribution of PP. Multivariate linear regression analysis was performed to assess the relationship between BMD and PP.

Results: A total of 8,179 NHANES participants were included in the study (Tables 1-3). The cohort's mean age (± SE) was 53.3 years 0.19, mean BMI (± SE) 29.6 kg/m^2 ± 0.07. PP was significantly higher with increased age, among Blacks (57.4 ± 0.52) and Hispanics (57.5 ± 0.19) compared to whites (53.9 ± 0.29), and for men (57.2 ± 0.16) when compared to women (54.1 ± 0.17), $p<0.05$. After adjusting for age, sex, race, menopause, body mass index, family history of osteoporosis, PP was associated with femoral neck BMD, $\beta=-0.0005$, $p<0.05$ but was not significantly associated with lumbar spine BMD, $\beta=-0.0002$, $p=0.07$.

Conclusion: Our results support the hypothesis that wide PP is associated with low BMD. This negative association was demonstrated at the femoral neck where bone loss and osteoporotic fractures occur at a more advanced stage, further supporting the relationship between atherosclerosis and osteoporosis risk. These findings have the potential for identifying high osteoporotic risk patients among those with wide pulse pressure, providing further indications for bone mineral density testing among these elderly frail patients. Further research is needed to investigate the mechanisms behind the relationship between PP and BMD.

Keywords: Osteoporosis; Cardiovascular disease; Bone mineral density; Pulse pressure; Femoral neck; Lumbar spine

Introduction

Osteoporosis and Cardiovascular Disease (CVD) are major public health problems, which are rapidly increasing as the population's ages. Osteoporosis causes more than 8.9 million fractures annually, equivalent to one fracture every 3 seconds [1], while CVD has been consistently the leading cause of death in the United States, accounting for more than a half million deaths every year [2].

Several lines of evidence exist regarding the association between osteoporosis and CVD. Previous studies and reviews have shown that these two diseases have common risk factors, such as aging, hypertension, dyslipidemia, smoking, alcohol abuse, and sedentary lifestyle [3,4]. Low bone mineral density is also associated with increased CVD morbidity and mortality [5]. Although these two conditions are seemingly unrelated and perhaps associations can be due to confounding factors, investigators have shown a number of interesting anatomical and pathophysiological features shared by both vascular system such as calcification and bone mineralization or remodelling [6]. For example, a recent meta-analysis demonstrated inverse relationship between hypertension and vitamin D levels, which is a key element in bone metabolism [7]. Moreover, many of medical treatments of osteoporosis or vascular disease have demonstrated a cross-benefit to one another; bisphosphonate for osteoporosis are associated with lower risk of coronary atherosclerotic disease [8,9] and statins to treat dyslipidemia are shown to decrease risk of osteoporotic fracture [10]. Similarly, decreased risk of fracture was associated with several antihypertensive drugs used to treat elderly hypertensive patients [11]. These reports suggest a complex and possibly interconnected pathophysiological pathways that form a common soil for two seemingly separate diseases.

Pulse Pressure (PP) is the difference between systolic and diastolic blood pressure. Wide PP is largely due to large-artery stiffness [12], while decreased PP is caused by low stroke volume, as in congestive heart failure or aortic valve stenosis [13]. Furthermore, there is increasing evidence that increased PP is an independent predictor of

risk of mortality from coronary heart disease as it is related to atherosclerosis [14-16]. Although PP is a readily-available measure calculated from any blood pressure reading, its value can often be overlooked as too non-specific.

In this context, we aim to examine association between PP and osteoporosis. Several studies have looked at positive correlation between osteoporosis and aortic stiffness including a study from our institution, where women with lower Bone Mineral Density (BMD) had increased arterial stiffness [17-20]. There have been research abstract and few studies to relate increased pulse wave velocity and osteoporosis but with limited study subjects number, region or race [21-23]. We aim to utilize National Health and Nutritional Examination Survey (NHANES) which is a nation-wide database that can provide essential and reliable data resource adequate for our study. We will examine relationship between PP and BMD, a surrogate measurement for osteoporosis.

Material and Methods

NHANES is a complex, multistage, area probability sample representative of the United States non-institutionalized civilian population (NHANES 2013). The interview, conducted in the home included questions on health and sociodemographic characteristics. After participating in the interview, respondents were invited to a mobile examination centre where standardized physical examinations were conducted, including blood pressure measurements. Data from 2 consecutive 2-year cycles of NHANES from 2009 to 2010 and 2011 to 2012 were used.

Blood pressure measurements were obtained in the mobile examination centre by trained physicians following a standard protocol. Appropriate blood pressure cuff sizes were used for participants based on measurement of midarm circumference. All blood pressure readings were obtained at a single examination visit. Pulse pressure calculation was made by subtracting the diastolic blood pressure from the systolic blood pressure reading. The average of ≤ 3 pulse pressure results was used for pulse pressure values. If there were only 1 or 2 readings, a single reading or the average of 2 readings were included in the analysis.

Bone Mineral Density (BMD) was measured by trained examiners in mobile examination centres. Total femoral bone density was measured by dual energy x-ray absorptiometry (Hologic QDR-1000; Hologic, Inc, Waltham, Mass). Scans were reviewed by consultants at the Mayo Clinic, Rochester MN, for quality control. BMD (grams per centimeter square) was measured by Dual Energy X-Ray Absorptiometry (DEXA). DEXA was administered to eligible survey participants in NHANES mobile examination centres. Women younger than 60 years were permitted to take the DEXA examination only if a pregnancy test taken at the time of the examination was negative. Individuals were excluded from the DEXA examination who reported taking tests with radiographic contrast material or having participated in nuclear medicine studies in the past 3 days or had a self-reported weight (>300 lb) or height (>6 ft 5 in) over the DEXA table limit. Whole-body DEXA scans were acquired using a QDR 4500A fan-beam densitometer (Hologic Inc.) following the manufacturer's acquisition procedures. Details of the DEXA protocol, quality control analysis, and multiple imputation procedure are available. We specifically examined lumbar spine BMD and total BMD. We chose lumbar BMD because the lumbar spine is one of the most common sites of fractures.

Statistical analyses were performed with linear regression procedures in SAS 7.3. We used sample weights when calculating point estimates, so estimates are representative of the civilian non-institutionalized US population at the time of NHANES 2011-2012. Weighted multivariate linear regression analyses were performed for the total sample and stratified by age (20-39 and 40-59 years). Models were adjusted for age at interview, race/ethnicity, BMI, diabetes, sleep duration and regular periods.

Results

A total of 8,179 NHANES participants were included in the study (Table 1). They were 55.2% women, with a mean age (± SE) 53.3 years ± 0.19, mean BMI (± SE) 29.6 kg/m^2 ± 0.07. Among women, the mean lumbar and femoral neck BMD were 1.00 ± 0.002 and 0.79 ± 0.002 respectively with a mean PP (± SE) of 54.1 ± 0.17.

Number of Study Subjects: 8,179	Lumbar Total BMD	Std Err	Femoral Neck BMD	Std Err	Pulse Pressure mmHg	Std Err
Men (44.8%)	1.064	0.0026	0.85	0.0026	57.2	0.16
Women (55.2%)	1	0.0023	0.79	0.0023	54.1	0.17
Age (years)						
20-39	1.06	0.0029	0.9	0.0034	45.54	0.29
40-59	1.04	0.0028	0.83	0.0026	48.83	0.3
60-79	1	0.0032	0.77	0.0029	65.16	0.27
≥ 80	1.01	0.0098	0.71	0.0062	73.71	0.3
Race						
White	1.03	0.0024	0.8	0.0023	53.9	0.29
Mexican	1	0.0039	0.83	0.0036	57.87	0.48
Other Hispanic	1.01	0.0056	0.81	0.0055	55.99	0.75
Black	1.09	0.0048	0.9	0.0048	57.43	0.52
Others	0.99	0.0077	0.8	0.0078	50.88	1.01
Smoking						
Current	1.04	0.0039	0.82	0.0029	53.29	0.24
Former	1.04	0.0037	0.79	0.0024	62.03	0.23
Never	1.02	0.0021	0.8	0.0021	57.95	0.18
Mean Age (All)	53.33	0.1868				
Mean BMI (All)	29.61	0.0692				

Table 1: Study Demographics

Men had higher BMD at the lumbar spine and femoral neck and higher PP compared to women. Lumbar BMD=1.064 ± 0.003, femoral neck BMD =0.85 ± 0.003, PP for men was 57.2 ± 0.16. The mean PP (mmHg) for women was 54.1 ± 0.17. Mean PP was significantly higher with increased age, among Blacks (57.4 ± 0.52), among all Hispanics (57.5 ± 0.19), compared to whites (53.9 ± 0.29) and for men (57.2 ± 0.16) when compared to women (54.1 ± 0.17), p<0.05 (Table 1).

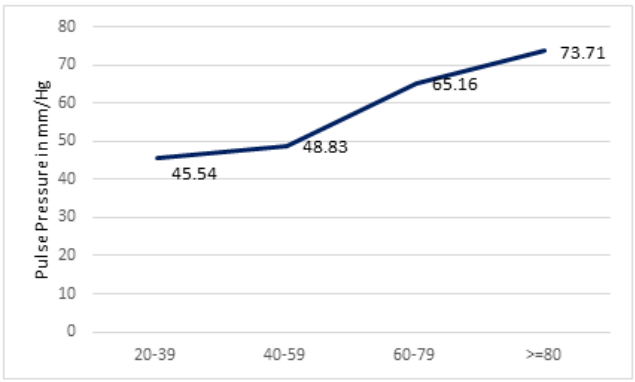

Figure 1: Mean pulse pressure by age groups.

	Q1	Q2	Q3	Q4	p
ALL	36.2 ± 5.26	47.9 ± 2.87	59.9 ± 4.36	87.2 ± 16.4	
Sex:					
Male	36.0 ± 5.17	48.0 ± 2.91	59.9 ± 4.31	84.7 ± 15.23	
Female	35.4 ± 5.66	47.8 ± 2.93	60.2 ± 4.41	87.4 ± 17.46	
Age:					
20-39 years	35.7 ± 5.26	47.5 ± 2.85	58.9 ± 4.12	78.5 ± 9.57	
40-59 years	35.3 ± 5.76	47.7 ± 2.93	59.2 ± 4.10	83.8 ± 16.40	<0.05
60-79 years	36.9 ± 4.87	48.2 ± 2.89	60.7 ± 4.46	84.8 ± 15.04	
≥ 80 years	37.0 ± 4.17	49.4 ± 2.72	61.0 ± 4.20	91.9 ± 19.43	
Race/Ethnicity:					
Mexican American	36.2 ± 5.26	47.9 ± 2.87	59.9 ± 4.36	87.2 ± 16.42	
Other Hispanic	35.8 ± 5.23	47.6 ± 2.94	60.0 ± 4.33	86.1 ± 16.72	
Non-Hispanic White	35.6 ± 5.40	48.0 ± 2.90	60.1 ± 4.40	85.8 ± 15.98	
Non-Hispanic Black	35.4 ± 5.91	48.1 ± 2.99	60.2 ± 4.33	87.2 ± 18.09	
Other	35.7 ± 5.23	47.5 ± 2.88	59.6 ± 4.28	83.2 ± 13.65	

Table 2: Quartile distribution of mean pulse pressure by age, sex and race.

A comparison between the overall mean PP and those within the 20-39, 40-59, and 50-79 age groups demonstrated a minimal difference. However, in the ≥ 80 age group the mean PP was consistently increased compared to the overall mean PP within all quartiles; reaching as high as 91.9 ± 19.43 in the 4th quartile among those who are ≥ 80 years of age. (Figure 1) Our study did not demonstrate significant difference among the different racial groups in the highest PP quartile. The lack of a significant difference between the races in the ≥ 80 years of age group could be explained by the fact that high risk minority groups suffer premature cardiovascular death compared with Whites, leaving a relative healthy non-White population with more or less equal PP observed (Table 2).

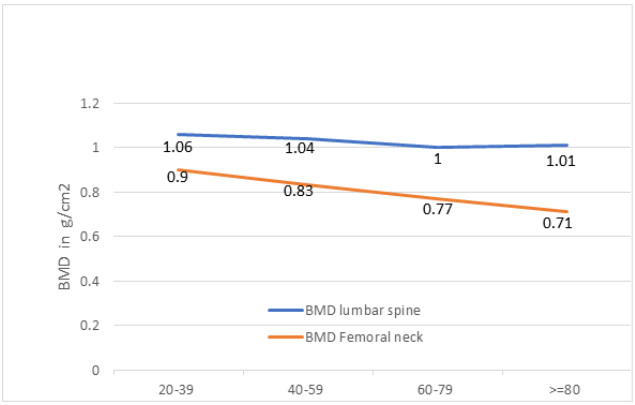

Figure 2: Mean bone mineral density among age groups.

	βEstimate	Standardized Estimate	p
Lumbar Spine			
Mean Pulse Pressure	-0.0002	-0.0305	0.07
Sex	0	0	1
Age	-0.0185	-0.1001	<0.05
Race	0.0036	0.0299	<0.05
Body Mass Index	0.0066	0.2948	<0.05
Family History of Osteoporosis	-0.0107	-0.023	0.11
Menopause (past 12 months)	-0.0864	-0.2669	<0.05
Femoral Neck			
Mean Pulse Pressure	-0.0005	-0.0788	<0.05
Sex	0	0	1
Age	-0.0374	-0.2284	<0.05
Race	0.0138	0.1187	<0.05
Body Mass Index	0.0078	0.3462	<0.05
Family History of Osteoporosis	-0.0119	-0.0275	<0.05
Menopause (past 12 months)	-0.0777	-0.2439	<0.05

Table 3: Linear regression results of pulse pressure, lumbar spine and femoral neck bone mineral density.

After adjusting for age, sex, race, menopause, body mass index, family history of osteoporosis, PP was associated with femoral neck

BMD, β=-0.0005, p<0.05 but was not significantly associated with lumbar spine BMD, β=-0.0002, p=0.07 (Table 3, Figure 2). After adjusting for age, sex, race, menopause, body mass index, family history of osteoporosis, PP was associated with femoral neck BMD, β=-0.0005, p <0.05 but was not significantly associated with lumbar spine BMD, β=-0.0002, p=0.07 (Table 3).

Discussion

Our results support the hypothesis that wide pulse pressure, a surrogate marker of atherosclerosis is associated with low BMD, a measurement for osteoporosis. This supports the notion of a related pathogenesis between osteoporosis and atherosclerosis as demonstrated in several reports including one by our group [4,19]. Several mechanisms have been proposed to explain the high risk for atherosclerosis among population with low BMD. These include increased cytokine production, recruitment of osteoclasts that lead to increased bone resorption, and loss of estrogen. Estrogens which have a favorable effect on nitric oxide function is beneficial for endothelial function as well as recruitment of osteoblasts, which at least partially explains the rapid bone loss after menopause [14,24]. This factor together with a decreased skin response to ultraviolet rays leads to decreased vitamin D generation and ultimately contributes to bone resorption [7]. Furthermore, hypertension, an established cause for atherosclerosis, has been associated with lower bone mineral density likely explained by increased calciuria [18]. Hypertensive women have low BMD compared to their normotensive counterparts even after adjusting for confounding factors including thiazide diuretic use. Thiazide diuretic use may mask subclinical-yet relevant-hyperparathyroidism in hypertensive patients which could also be thought to increase bone resorption in those hypertensive patients [25].

Rat models have demonstrated hypertensive rats have higher urinary calcium compared to wild type animals. These animal studies also support the notion that hypertension may lead to a transient serum hypocalcemia and further promote bone resorption to maintain calcium homeostasis [26]. Dyslipidemia, a major contributor to atherosclerosis is also associated with lower bone density [27]. In fact, oxidized LDL, not only leads to atherosclerotic plaques, but also inhibits osteoblasts. Not surprisingly, statins, agents that decrease this oxidized LDL-cholesterol are associated with higher bone mineral density [28]. Population studies from Finland demonstrated that statin use is associated with increased BMD in women [29]. On the other hand, bisphosphonates, agents used for treatment of osteoporosis are associated with favorable lipid profile. These agents work one step downstream from the HMG-CoA reductase in the mevalonate pathway [5,30]. Statins have mainly target the mevalonate pathway in the liver to decrease lipid synthesis, while bisphosphonates have target mevalonate pathway in the bone and are the mainstay for therapy for osteoporosis [31,32]. On-going research is likely to develop agents with equal affinities for bone and liver, thus treating both osteoporosis and atherosclerotic disease, common co-morbid conditions among elderly population with one therapeutic agent [33].

Our study based on NHANES data, has several limitations such the lack of contemporaneous vitamin D, parathyroid, calcitonin levels with BMD measurements. These metabolic makers could have help identified other metabolic derangements that could explain the findings on BMD encountered in the elderly population, the age group known at highest risk for Vitamin D deficiency. Other limitations include lack of data on personal history of fracture as well as maternal fracture etc. that might account for low bone mass independent of the high pulse pressure.

Conclusion

Finally, our study demonstrated a negative association between low cortical bone and pulse pressure. Additional studies are needed to confirm our findings and to elucidate the mechanisms underlying this association. Our study also has the potential for identifying patients with high pulse pressure for potential screening for osteoporosis through BMD measurements which help prevent fractures, particularly at the hip, a devastating and most feared consequence of osteoporosis that is associated with increased morbidity and mortality among older frail populations.

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