Original Article

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Investigating the association between creatinine-adjusted urinary catecholamines and site-specific bone mineral density in older adults

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Abstract

Objectives: Osteoporosis is common among older adults, but the relationship between neuroendocrine factors – particularly catecholamines – and bone mineral density (BMD) is not well understood. This study examined associations between catecholamine levels and BMD in older adults.

Methods: Data from the 2017–2022 biomarkers wave of the Midlife in the United States (MIDUS 3) study were analyzed. Multiple linear regressions assessed associations between creatinine-adjusted urinary norepinephrine and epinephrine levels and BMD at the lumbar spine (L1–L4), right and left total femur, and one-third radius. Models adjusted for age, sex, body mass index (BMI), smoking history, diet, medications (thiazide diuretics, phosphate binders, beta blockers, and vitamin D analogues), and serum creatinine.

Results: Among 324 participants (41 % male; mean age 64.3±9.3 years), higher epinephrine levels were significantly associated with lower lumbar spine BMD (Beta=−0.122; 95 % CI: [−0.242 to −0.003], p=0.045), while norepinephrine showed no association (p=0.865). No significant relationships were observed at femoral or radial sites, though norepinephrine was marginally linked to lower one-third radius BMD (Beta=−0.087; 95 % CI: [−0.176 to 0.002], p=0.055). Male sex and higher BMI predicted greater BMD (p<0.05), whereas older age was linked to lower femoral and radial BMD (p<0.05).

Conclusions: Elevated epinephrine levels are associated with reduced lumbar spine BMD in older adults, and elevated norepinephrine levels are associated with reduced distal radius BMD, suggesting catecholamines may influence bone metabolism in a site-specific manner relevant to osteoporosis pathophysiology.

Keywords: neuroendocrine measures; catecholamines; bone mineral density; osteoporosis

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Introduction

Maintaining bone health in older adults is crucial, as age-related reductions in bone density substantially increase fracture risk, leading to disability and diminished quality of life [1]. Osteoporosis is a major contributor to morbidity in this population, with an estimated global prevalence of 21.7 % [2]. Osteoporotic fractures, particularly hip fractures, are associated with high mortality, with some studies reporting a 19 % mortality rate within the first year post-fracture [3].

Advancing age and postmenopausal status are well-established risk factors for osteoporosis [4]; however, secondary causes, which act independently of age or estrogen

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deficiency, also contribute to skeletal fragility [5]. Previous studies have identified multiple risk factors, including prior fractures [6], low body mass index (BMI) [7], reduced physical activity [8], and thyroid dysfunction [9]. Beyond these predictors, emerging evidence indicates that molecular and hormonal regulators play critical roles in bone homeostasis, linking systemic and neuroendocrine processes to skeletal fragility. Chronic psychological stress, for instance, elevates circulating stress hormones that can enhance bone resorption [10]. Dopaminergic degeneration, as seen in Parkinson's disease, has been associated with decreased bone mineral density (BMD) due to altered bone remodeling [11]. Exogenous glucocorticoid exposure is another well-recognized contributor to secondary osteoporosis, prompting specific recommendations for screening and management in affected individuals [12]. Additionally, both experimental and clinical evidence suggest that adrenal hormone excess adversely affects skeletal health [13].

Pharmacological interventions aimed at reducing bone resorption in the elderly have been extensively studied. Bisphosphonates are among the most commonly prescribed agents [14]. Targeting hormonal activity has also garnered interest in recent years. Beta-blockers, for example, have been associated with higher BMD in a dose-dependent manner, regardless of beta-1 selectivity or duration of use [15]. Beta-1-selective beta-blockers, in particular, have been linked to increased lumbar spine BMD in postmenopausal women [16].

Considering these findings, there is a need for clinical research exploring the role of neuroendocrine hormones, specifically catecholamines, in osteoporosis pathophysiology in older adults. Furthermore, insights from experimental interventional studies support the importance of understanding mechanisms by which certain agents reduce bone resorption. Therefore, this study aimed to assess the association between creatinine-adjusted urinary catecholamine levels and BMD in an elderly population.

Materials and methods

Study population

The Midlife in the United States (MIDUS) study is a longitudinal cohort initiated in 1995, surveying over 7,000 adults aged 25–75 years on general health, with oversampling from five metropolitan areas. The study was designed to assess psychological, behavioral, and social determinants of age-related physical and mental health. Follow-up waves included MIDUS2 in 2009 and MIDUS3 in 2013, both of which incorporated biomarker data collection. For MIDUS3, biomarker data collection commenced in 2017. Participants attended a 24-h research visit at one of three sites (UCLA, University of Wisconsin–Madison, or Georgetown University), during which musculoskeletal, neurological, immune, and other systems were assessed. Trained clinicians collected all specimens required for biomarker analyses on-site.

The MIDUS3 biomarker project invited 747 participants (644 from the longitudinal survey sample and 103 from the Milwaukee sample), achieving an adjusted response rate of 64.3 % (747/1162). For this analysis, only 324 participants were included, as BMD measurements via Lunar DXA systems were available exclusively at the University of Wisconsin.

Study design

This cross-sectional study utilized data derived solely from the MIDUS3 Biomarker 2017–2022 dataset.

Study variables

Twelve-hour overnight (19:00–07:00) urine samples were assayed at the University of Wisconsin–Madison's Institute for Clinical and Translational Research (ICTR, Madison, WI) for catecholamines (norepinephrine, epinephrine, dopamine). Creatinine-adjusted urinary norepinephrine and epinephrine levels were quantified using high-performance liquid chromatography with electrochemical detection (HPLC-ECD) via a Dionex Ultimate 3000 electrochemical detection system (Thermo Scientific, Waltham, MA) following lab-based methodology using a Dionex Ultimate 3000 electrochemical detection system (Thermo Scientific, Waltham, MA) [17, 18]. Creatinine adjustment was calculated as (catecholamine μg/dL)/(urine creatinine mg/d × 0.001), as detailed in the MIDUS3 Biomarkers project documentation [19].

Dependent variables included BMD at the lumbar spine (L1–L4), right and left total femur, and one-third radius, measured using Lunar DXA scans. T-scores were recorded for all participants regardless of menopausal status or age. Scanning followed a prespecified protocol to ensure consistency; full procedural details are available in the MIDUS3 musculoskeletal health and function documentation [19].

Covariates included age, sex, history of regular smoking, BMI, dietary habits, use of medications that may affect BMD (thiazide diuretics, phosphate binders, beta blockers, and vitamin D analogues), and serum creatinine levels. Serum creatinine was assayed by Meriter Laboratories (Madison, WI), with methodology described in the MIDUS3 blood, urine, and saliva data documentation [19]. Dietary habits were assessed using questions on weekly frequency of consuming healthy foods (vegetables, fruits, lean meats, fish, whole grains) and unhealthy foods (fast food, fatty foods,

sugary beverages), generating a MIDUS Healthy Eating Index (HEI) score ranging from 0 to 11, with higher scores indicating healthier habits.

Statistical analysis

Descriptive statistics summarized participant characteristics. Continuous variables were presented as means±standard deviation (SD) for normally distributed variables and medians with interquartile range (IQR) for non-normal ones; categorical variables were expressed as counts and percentages. Associations between creatinine-adjusted urinary catecholamine levels and BMD at different skeletal sites were examined using multiple linear regression models, with separate models for each site. All models adjusted for the covariates listed above. Regression results are reported as standardized beta coefficients (β) with 95 % confidence intervals (CI). A p-value <0.05 was considered statistically significant. Analyses were conducted using Jamovi software (Version 2.6.13, 2024; https://www.jamovi.org), one of the software used in medical research statistical analyses [20].

Ethical approval

This study constitutes a secondary analysis of publicly available MIDUS data. All MIDUS protocols were approved by the University of Wisconsin–Madison Institutional Review Board.

Results

Following the inclusion of participants who underwent BMD assessment, the total number of participants was 324, with 41 % being males and a mean age of 64.3 years (SD=9.3). Also, 48 % of participants had a history of regular smoking. Descriptives of controlled variables, alongside the descriptives for different BMD indices, are displayed under Tables 1 and 2.

Multiple linear regression analysis revealed significant decrease in lunar spine BMD by creatinine-adjusted urine epinephrine level (Beta=−0.122; 95 % CI: [−0.242 to −0.003], p=0.045), but not by creatinine-adjusted urine norepinephrine levels (p=0.865). Among controlled covariates, sex and BMI owed significant associations. Females had significantly lower BMD (Beta=−0.63; 95 % CI: [−0.863 to −0.397], p<0.001) and higher BMI predicted higher BMD (Beta=0.285; 95 % CI: [0.173 to 0.397], p<0.001). See Table 3. Of note, the model had acceptable model fit indices, with statistical assumptions being met and absence of multicollinearity.

Table 1: Descriptives of continuous controlled variables and different BMD indices in elderly.

	Mean	SD
Age, years	64.4	9.3
MIDUS HEI score	5.1	1.5
BMI, kg/m^2	31.4	7.2
Lunar spine L1-4 bone mineral density, g/cm^2	1.3	0.3
Lunar LEFT total femur (BMD) bone mineral density, g/cm^2	1	0.2
Lunar RIGHT total femur (BMD) bone mineral density, g/cm^2	1	0.2
Lunar radius 1/3 (BMD) bone mineral density, g/cm^2	0.9	0.2

	Median	25th percentile	75th percentile
Urine norepinephrine (creatinine-adjusted), ug/g[a]	25.6	16.4	35.5
Urine epinephrine (creatinine-adjusted), ug/g[a]	3.7	2.3	6.1
Creatinine, mg/dl[a]	0.9	0.8	1

[a]Not normally distributed.

Table 2: Descriptives of categorical controlled variables in elderly.

Sex	Counts	% Of total
Male	134	41 %
Female	190	59 %
History of regular smoking		
Yes	155	48 %
No	169	52 %
Medications: Beta blocker (beta-1-selective) use		
Yes	52	17 %
No	249	83 %
Diuretic thiazide use:		
Yes	42	14 %
No	259	86 %
Phosphate binder use:		
Yes	20	7 %
No	281	93 %
Vitamin D analogue use:		
Yes	92	31 %
No	209	69 %

Table 4 shows how catecholamines predict Femur BMD. As seen, no significant association was seen between epinephrine or norepinephrine with BMD. However, sex, age, and BMI had significant prediction. Of note, both models had acceptable model fit indices, with statistical assumptions being met and absence of multicollinearity.

Table 3: Multiple linear regression analysis for the prediction of urinary catecholamines for lunar spine L1–L4 bone mineral density (g/cm^2) in elderly.

Spine L1–L4 BMD	95 % confidence interval			
Predictor	**Beta**	**Lower**	**Upper**	**p-Value**
Sex:				
Female – male (Ref)	−0.63	−0.863	−0.397	<0.001
Smoking history:				
No – yes	0.208	−0.009	0.426	0.061
Age	0.048	−0.065	0.161	0.407
MIDUS HEI	−0.002	−0.113	0.109	0.967
BMI	0.285	0.173	0.397	<0.001
Creatinine	0.083	−0.035	0.201	0.165
Urine norepinephrine (creatinine-adjusted)	0.01	−0.107	0.127	0.865
Urine epinephrine (creatinine-adjusted)	−0.122	−0.242	−0.003	0.045
Beta blocker (beta-1-selective) use:				
No – yes	0.137	−0.158	0.431	0.361
Diuretic thiazide use:				
No – yes	0.11	−0.205	0.426	0.493
Phosphate binder use:				
No – yes	0.027	−0.443	0.497	0.91
Vitamin D analogue use:				
No – yes	0.128	−0.11	0.366	0.291

R^2=0.236 (n=274).

Regarding radius distal third BMD, Table 5 shows how catecholamines predict the density. As seen, none of catecholamines had significant prediction. However, higher norepinephrine levels predicted lower density with p-value close to but not reaching-the significance level (Beta=−0.087; 95 % CI: [−0.176 to 0.002], p=0.055). Among covariates, female sex (Beta=−1.239, 95 % CI: [−1.417 to −1.061], p<0.001]), age (Beta=−0.258; 95 % CI: [−0.344, −0.171], p<0.001), and BMI (Beta=0.291; 95 % CI: [0.206 to 0.376], p<0.001) significantly predicted the Radius 1/3 BMD. Of note, the model had acceptable model fit indices, with statistical assumptions being met and absence of multicollinearity.

Discussion

Our findings demonstrate region-specific associations between catecholamines and bone mineral density (BMD) in

Table 4: Multiple linear regression analysis for the prediction of urinary catecholamines for lunar right and left total femur bone mineral density (g/cm^2) in elderly.

Lunar left total femur BMD	95 % confidence interval			
Predictor	**Beta**	**Lower**	**Upper**	**p-Value**
Sex:				
Female – male (Ref)	−0.713	−0.932	−0.494	<0.001
Smoking history				
No – yes	0.196	−0.009	0.4	0.061
Age	−0.213	−0.319	−0.106	<0.001
MIDUS HEI	0.072	−0.032	0.176	0.171
BMI	0.428	0.325	0.532	<0.001
Creatinine	0.036	−0.074	0.147	0.519
Urine norepinephrine (creatinine-adjusted)	0.013	−0.097	0.122	0.817
Urine epinephrine (creatinine-adjusted)	−0.063	−0.175	0.049	0.272
Beta blocker (beta-1-selective) use:				
No – yes	0.172	−0.104	0.447	0.22
Diuretic thiazide use:				
No – yes	0.086	−0.202	0.374	0.557
Phosphate binder use:				
No – yes	0.031	−0.392	0.454	0.884
Vitamin D analogue use:				
No – yes	0.084	−0.141	0.309	0.464
Lunar right total femur BMD	**95 % confidence interval**			
Predictor	**Beta**	**Lower**	**Upper**	**p-Value**
Sex:				
Female – male (Ref)	−0.721	−0.949	−0.492	<0.001
Smoking history				
No – yes	0.169	−0.044	0.382	0.119
Age	−0.185	−0.295	−0.075	0.001
MIDUS HEI	0.058	−0.051	0.166	0.294
BMI	0.378	0.27	0.486	<0.001
Creatinine	0.042	−0.073	0.157	0.472
Urine norepinephrine (creatinine-adjusted)	−0.019	−0.133	0.094	0.739
Urine epinephrine (creatinine-adjusted)	−0.031	−0.148	0.085	0.598
Beta blocker (beta-1-selective) use:				
No – yes	0.214	−0.072	0.5	0.142
Diuretic thiazide use:				
No – yes	0.024	−0.276	0.324	0.876

Table 4: (continued)

Lunar right total femur BMD	95 % confidence interval			
Predictor	**Beta**	**Lower**	**Upper**	**p-Value**
Phosphate binder use:				
No – yes	0.134	−0.307	0.575	0.549
Vitamin D analogue use:				
No – yes	0.029	−0.207	0.264	0.811

R^2=0.357 (n=263).
R^2=0.302 (n=264).

Table 5: Multiple linear regression analysis for the prediction of urinary catecholamines for lunar radius (1/3) bone mineral density (g/cm^2) in elderly.

Lunar radius 1/3 BMD	95 % confidence interval			
Predictor	**Beta**	**Lower**	**Upper**	**p-Value**
Sex:				
Female – male, Ref	−1.239	−1.417	−1.061	<0.001
Smoking history				
No – yes	0.122	−0.044	0.288	0.149
Age	−0.258	−0.344	−0.171	<0.001
MIDUS HEI	−0.037	−0.122	0.047	0.382
BMI	0.291	0.206	0.376	<0.001
Creatinine	0.051	−0.039	0.141	0.27
Urine norepinephrine (creatinine-adjusted)	−0.087	−0.176	0.002	0.055
Urine epinephrine (creatinine-adjusted)	−0.01	−0.102	0.081	0.821
Beta blocker (beta-1-selective) use:				
No – yes	0.093	−0.131	0.316	0.415
Diuretic thiazide use:				
No – yes	−0.061	−0.3	0.178	0.615
Phosphate binder use:				
No – yes	0.139	−0.213	0.491	0.439
Vitamin D analogue use:				
No – yes	0.033	−0.149	0.215	0.72

R^2=0.552 (n=277).

older adults. Notably, higher urinary epinephrine levels were linked to lower lumbar spine (L1–L4) BMD, consistent with previous clinical observations. For instance, a study in Puerto Rican adults reported that elevated urinary epinephrine correlated with reduced lumbar spine BMD, with men exhibiting higher odds of osteoporosis (OR=4.01) [21]. Of note, our study had an older adult's cohort, which constitutes a major difference with that study. Similarly, patients with pheochromocytoma or paraganglioma, conditions characterized by chronically elevated catecholamines, exhibited impaired trabecular bone scores and bone quality, which improved following tumor removal [22]. Laboratory studies further support these associations, demonstrating that β-adrenergic activation promotes osteoclast activity via RANKL signaling and oxidative stress, thereby accelerating bone loss [23]. These findings underscore the role of adrenergic activity in trabecular-rich regions such as the spine and suggest that urinary epinephrine may serve as a predictive marker of osteoporosis risk in older adults.

Our results also provide mechanistic insight into experimental studies examining neuroendocrine regulation of bone remodeling. Evidence indicates that beta-adrenergic pathways influence bone metabolism via central nervous system signaling and that beta-blockers may exert protective effects on bone [24]. Animal studies consistently support this concept: non-selective beta-blockers have been shown to enhance bone mass in wild-type and ovariectomized mice, a well-established model for postmenopausal osteoporosis [25]. Furthermore, combined administration of beta-blockers and intermittent parathyroid hormone (PTH) improved bone mass and microarchitecture in ovariectomized mice, suggesting synergistic effects on bone formation [26]. In humans, selective beta-blockers, rather than non-selective agents, have been associated with higher BMD [27, 28]. Our data provide a plausible explanation: both epinephrine and, to a lesser extent, norepinephrine (p=0.055) were inversely associated with BMD at the lumbar spine and distal radius. Accordingly, pharmacological inhibition of catecholamine activity may increase BMD at specific sites by reducing bone resorption.

Despite these findings, urinary catecholamine levels were not associated with total femur BMD, either on the right or left side. This discrepancy may be attributed to differences in bone composition, which is broadly classified into cortical and trabecular types. Trabecular bone comprises approximately 20 % mineralized tissue, with the remaining volume occupied by bone marrow and adipose tissue. Compared with cortical bone, trabecular bone contains less calcium, more water, and a larger surface area in contact with marrow and blood vessels, resulting in higher metabolic activity and turnover rates [29]. The lumbar spine and distal radius are prototypical trabecular-rich sites, overlaid by a thin cortical shell. Understanding these regional microstructural variations is essential for assessing bone loss and provides insight into the mechanisms underlying fracture risk [30], as well as the site-specific effects of

catecholamines on BMD observed in our study. Distal radius fractures are among the most common osteoporotic fractures, with over 640,000 cases occurring annually in the United States, representing a significant economic and clinical burden [31]. In contrast, the femoral shaft is predominantly cortical bone, characterized by higher density, lower metabolic activity, and slower turnover [29]. Supporting this, a U.S. cross-sectional study of 3,358 men aged 65–100 years demonstrated substantial reductions in trabecular BMD at the femoral neck among the oldest participants (≥85 years), while cortical BMD along the femoral shaft remained largely preserved [32]. These findings suggest that cortical bone is relatively resistant to catecholamine-mediated bone loss, which likely explains the absence of significant associations between urinary catecholamines and femoral BMD in our study. Nevertheless, it is still a little bit unclear why urinary epinephrine performs much better than urinary norepinephrine, and further research is needed for the determination of molecular effects.

Consistent with prior research, higher BMI was positively associated with BMD across all regions, with the strongest effects observed at the femur, followed by the lumbar spine and distal radius. This pattern mirrors previous studies showing that women in the lowest BMI tertiles experience nearly twice the bone loss at the spine and hip compared with those in the highest tertiles ($p<0.001$) [33]. Weight-bearing sites, such as the femur and spine, are particularly responsive to BMI-related mechanical loading, whereas non–weight-bearing sites like the distal radius are less affected [34]. Mechanistically, the protective effects of higher BMI may involve direct skeletal loading and increased aromatization of adrenal androgens in adipose tissue [35, 36].

Sex differences in BMD were also observed, with women exhibiting lower values across all examined sites, consistent with the literature [37, 38]. These differences reflect the critical role of estrogen deficiency in osteoporosis pathogenesis, with more pronounced effects in women during menopause [39, 40].

We observed that advancing age was associated with lower BMD at the right and left total femur as well as the distal one-third radius, whereas lumbar spine (L1–L4) BMD was not significantly influenced by age. These findings are consistent with prior literature documenting age-related declines in both trabecular and cortical femoral BMD, with some evidence of sex-specific differences [32, 41]. Similarly, previous studies have reported decreasing BMD at the distal third of the radius with advancing age [42]. In contrast, lumbar spine BMD appears less affected by age. For example, a study involving over 1,440 women (mean age 66.7 years) reported a 2.6 % increase in lumbar spine BMD between ages 62.5 and 77.5, despite a decline in the preceding decade [43]. Longitudinal analyses further indicate that bone loss at the lumbar spine is most pronounced in the early postmenopausal period (<10 years since menopause), subsequently plateauing in later years [44]. Interestingly, these studies suggest that hip and forearm sites, but not the spine, show the strongest concordance between cross-sectional and longitudinal age-related BMD changes. Collectively, these findings support our observations and underscore the need for further research into the mechanisms, including catecholamine-mediated pathways, underlying site-specific BMD changes in older adults.

In addition, participants without a history of smoking exhibited higher lumbar spine (L1–L4) and left total femur BMD, although close to not statistically significant ($p=0.061$). This finding is particularly relevant given the high prevalence of smoking globally and in countries such as Jordan, where rates reach 65 % among men and 17 % among women [45]. Smoking is also associated with an indirect substantial burden of low back pain, which is highly prevalent in osteoporotic populations [46] and affected over 271 million adults aged 55 and older worldwide in 2021 [47], negatively impacting health-related quality of life [48]. By promoting spinal bone loss, smoking exacerbates osteoporosis and subsequently low back pain. Importantly, smoking cessation has been shown to reverse these effects and improve BMD [49], highlighting the potential of targeted interventions to reduce fracture risk. These results emphasize the urgent need to address smoking as a modifiable risk factor. Public health strategies aimed at reducing tobacco use could help preserve lumbar spine BMD, decrease the incidence of low back pain, and improve overall population health outcomes.

In conclusion, our study provides novel insights into the associations between catecholamines and BMD in older adults, highlighting region-specific effects. These results emphasize the importance of further research examining the impact of beta-adrenergic receptor modulation, as well as other potential therapeutic interventions, on osteoporosis prevention and management in the elderly population.

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Research ethics: This research represents a secondary analysis of publicly available MIDUS data. The University of Wisconsin–Madison Institutional Review Board (IRB) approved all MIDUS study protocols.

Informed consent: Not applicable.

Author contributions: LA: Contributed to conceptualization, data acquisition, formal analysis, project administration and supervision. MK, RM, HB: Reviewed relevant literature, identified gaps in current knowledge, provided critical input in formulating the research objectives and overall study concept, and drafted sections of the original manuscript linking the literature to the study rationale. MZ, RS, SH, OA, AA, QF, and MS: Interpreted the study results, emphasized the significance of the findings within the context of existing literature, and drafted the sections addressing study implications and related content. All authors validated the results, reviewed and approved the final version of the manuscript, and are accountable for all aspects of the work. The sequence of author's names was based on their scientific contributions and was approved by all authors.

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