Original Investigation / Orijinal Araştırma

DOI: 10.4274/tod.galenos.2024.05826
Turk J Osteoporos 2025;31(1):6-11

The Relationship Between Bone Mineral Density and Sympathetic Skin Response in Postmenopausal Women

Postmenapozal Kadınlarda Kemik Mineral Yoğunluğu ile Sempatik Deri Yanıtı Arasındaki İlişki

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Abstract

Objective: Osteoporosis (OP) is a common condition characterized by decreased bone mass. The sympathetic nervous system is involved in bone remodeling and vasomotor symptoms in postmenopausal women. This study aimed to assess the relationship, using sympathetic skin response (SSR) measurements, between autonomic dysfunction and OP in postmenopausal women experiencing vasomotor symptoms.
Materials and Methods: A total of 101 postmenopausal women aged 45-65 with complaints of hot flashes and sweating were included. The study was a single-center, cross-sectional, observational investigation. Based on dual-energy X-ray absorptiometry results, participants were categorized into OP, osteopenia, and normal groups. SSR latencies and amplitudes, recorded bilaterally from hands and feet, were compared among the groups. Correlations between bone mineral density (BMD) and SSR results were analyzed.
Results: There were no significant differences in SSR latencies between the groups (p>0.05). Although SSR amplitudes were lowest in the OP group, the differences were not statistically significant (p>0.05). No significant correlation was found between BMD scores and SSR measurements (p>0.05).
Conclusion: The study found no association between autonomic dysfunction, as indicated by SSR responses, and BMD scores in postmenopausal women.
Keywords: Sympathetic skin response, bone mineral density, autonomic dysfunction, osteoporosis

Öz

Amaç: Osteoporoz (OP), azalmış kemik kütlesi ile karakterize edilen yaygın bir durumdur. Sempatik sinir sistemi, postmenopozal kadınlarda hem kemik yeniden şekillenmesinde hem de vazomotor semptomların gelişiminde rol oynar. Bu çalışma, vazomotor semptomlar yaşayan postmenopozal kadınlarda sempatik deri yanıtı (SDY) ölçümleri kullanılarak, otonomik disfonksiyon ile OP arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır.
Gereç ve Yöntem: Çalışmaya, sıcak basması ve terleme şikayeti olan 45-65 yaş arası toplam 101 postmenopozal kadın dahil edilmiştir. Çalışma, tek merkezli, kesitsel ve gözlemsel bir araştırma olarak tasarlanmıştır. Dual enerji X-ışını absorpsiyometrisi sonuçlarına göre katılımcılar OP, osteopeni ve normal gruplara ayrılmıştır. SDY latans ve amplitüd değerleri ellerden ve ayaklardan bilateral olarak kaydedilmiş ve gruplar arasında karşılaştırılmıştır. Kemik mineral yoğunluğu (KMY) ile SDY sonuçları arasındaki korelasyonlar analiz edilmiştir.
Bulgular: Gruplar arasında SDY latans değerlerinde anlamlı bir fark bulunmamıştır (p>0,05). SDY amplitüdleri OP grubunda en düşük olmasına rağmen, bu fark istatistiksel olarak anlamlı değildir (p>0,05). KMY skorları ile SDY ölçümleri arasında da anlamlı bir korelasyon bulunmamıştır (p>0,05).
Sonuç: Çalışma, postmenopozal kadınlarda SDY yanıtları ile KMY skorları arasında otonomik disfonksiyon göstergesi olabilecek bir ilişki tespit edememiştir.
Anahtar kelimeler: Sempatik deri yanıtı, kemik mineral yoğunluğu, otonomik disfonksiyon, osteoporoz

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Received/Geliş Tarihi: 12.07.2024 **Accepted/Kabul Tarihi:** 23.09.2024 **Publication Date/Yayınlanma Tarihi:** 20.03.2025

Cite this article as/Atıf: Çelik G, Sarı MH, Bilgilisoy Filiz M, Koldaş Doğan Ş. The relationship between bone mineral density and sympathetic skin response in postmenopausal women. Turk J Osteoporos. 2025;31(1):6-11

Introduction

Osteoporosis (OP) is a prevalent condition characterized by microstructural deterioration in bone tissue and progressive loss of bone mass. Hormonal factors, nutritional status, and biomechanical stress regulate the remodeling process of bone. Systemic hormones and local factors also regulate osteoblastic and osteoclastic activities (1,2).

There is evidence of a close relationship between the sympathetic nervous system and bone metabolism. Several studies have suggested that the sympathetic nervous system mediates bone remodeling. Norepinephrine binds to beta (β)2-adrenergic receptors specifically found in osteoblasts, inhibiting osteoblast activity and thereby impeding bone formation. Additionally, adrenergic nerves can activate the receptor activator of nuclear factor-kappa B ligand (RANKL) in osteoblasts, triggering RANKL-mediated osteoclastogenesis and bone resorption (3,4). Leptin, one of the hormones involved in regulating norepinephrine release, exerts anti-osteogenic effects by binding to hypothalamic receptors (5). An animal study demonstrated that the infusion of leptin into the third ventricle reduced bone mass and bone formation parameters, highlighting its critical role in the regulation of bone formation (6).

The role of the sympathetic system in investigating postmenopausal OP has been explored using ovariectomized mouse models. The β-adrenergic blockade, when applied in adult mice following ovariectomy, has partially mitigated bone loss by preventing a general decrease in bone mineral density (BMD) (7). Clinical observations on postmenopausal women have yielded similar findings. The use of β-blockers in postmenopausal individuals has been correlated with higher BMD scores, demonstrating associations with better trabecular microarchitecture in the femur length and lumbar spine (8,9).

Vasomotor symptoms (such as hot flashes and night sweats) are pronounced in postmenopausal women. It is known that the autonomic dysfunction arising from a decrease in estrogen levels is linked to high sympathetic activation (10). On the other hand, studies have found an association between decreased bone mass and vasomotor symptoms in postmenopausal women (11).

Sympathetic skin response (SSR) is a neurophysiological examination used to assess vasomotor and sudomotor activity stimulated by cholinergic sympathetic fibers of the autonomic nervous system (12). SSR has been employed to demonstrate the role of sympathetic function in various diseases within neurological, dermatological, and rheumatological fields (13-17). During the examination, responses are recorded from the palmar and plantar surfaces, where sweat glands are most densely distributed (18). The study aimed to investigate the relationship between BMD and SSR in postmenopausal women with autonomic dysfunction.

Materials and Methods

Study Design

The study was designed as a single-center cross-sectional investigation at the University of Health Sciences Türkiye, Antalya Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation between June 2022 and December 2022. Before commencing the study, approval was obtained from the Clinical Research Ethics Committee of the Health Sciences University of Türkiye, Antalya Training and Research Hospital on March 31, 2022, with decision number 7/17. Our study adheres to the principles of the 2013 Helsinki Declaration. Informed voluntary consent was obtained from participants by signing an informed consent form. The sample size was calculated using G-Power 3.1.9.4 software, considering an effect size (f) of 0.3, α of 0.05, and power of 0.80 for each group, resulting in a total of 84 volunteers (28 per group).

Participants

The study included 120 postmenopausal women aged 45-65 years who applied to the physical medicine and rehabilitation outpatient clinic for various reasons and reported experiencing hot flashes and sweating once a day. Exclusion criteria comprised a history of systemic diseases (diabetes mellitus, coronary artery disease, hypertension, thyroid dysfunction), neurological disorders (cerebrovascular diseases, polyneuropathy), secondary OP, collapse fractures, malignancy, regular medication use (including calcium-channel blockers, β-blockers, glucocorticoids, anti-diabetic agents, anti-resorption agents, anti-arrhythmia agents, oral contraceptives, anti-coagulants), psychiatric diseases, and inflammatory rheumatic diseases. Fourteen patients meeting the exclusion criteria and five patients unwilling to participate voluntarily were excluded from the study. A total of 101 patients were categorized into three groups based on dual-energy X-ray absorptiometry (DEXA) results: those with a T-score of -2.5 standard deviations (SDs) or below were classified as having OP, those with T-scores between -1 and -2.5 SD had osteopenia, and those with T-scores above -1 SD were considered normal (19). The BMD of the lumbar spine, femoral neck, and total hip was assessed using DEXA (Lunar DPX-L model, Lunar, Madison, Wisconsin, USA).

Outcome Measures: Sympathetic Skin Response

SSR was conducted using an electroneuromyography device (Nihon Kohden Neuropack S1 MEB-9400K) in a quiet room with a temperature between 22 °C and 24 °C. Patients were positioned in a supine posture, and skin temperatures were maintained at 32 °C. Active electrodes were placed on the palmar surface of the hand and the plantar surface of the foot, while reference electrodes were placed on the dorsal surface of the hand and foot. To prevent habituation, stimuli of irregular intervals lasting more than a minute were applied at 20-30 mA.

When habituation occurred, the stimulus was delayed by five minutes. Skin potentials were analyzed for 10 seconds, and the average value was recorded. Latency was measured in seconds, considering the onset of the first negative deflection, and amplitude was measured in millivolts as peak to peak.

Statistical Analysis

SPSS version 25.0 for Windows was used for the analyses. The assumption of normality was assessed using the Shapiro-Wilk test. One-way analysis of variance was applied for data exhibiting parametric distribution, while the non-parametric Kruskal-Wallis test was utilized for non-normally distributed data. Pearson correlation was used for relationships among variables demonstrating normality, and Spearman correlation was employed for relationships among variables not meeting the assumption of normality. A significance level of $p<0.05$ was considered statistically significant in the analyses of the obtained data.

Results

The mean ages were 56.76±5.36 years in the osteoporotic group, 56.19±6.06 years in the osteopenic group, and 53.52±4.21 years in the normal group. There was a statistically significant difference in age and body mass index (BMI) among the groups ($p<0.05$). In the OP group, the average age was higher, and the BMI was higher in the normal group. There was no statistically significant difference in demographic characteristics, including menopausal age and menopausal duration, among the groups ($p>0.05$) (Table 1).

There was no statistically significant difference among the groups in the mean latencies of SSR recorded from the hands and feet ($p>0.05$). Although the mean amplitude of SSR was the lowest in the osteoporotic group, it was not statistically significant ($p>0.05$) (Table 2).

There was no statistically significant correlation between the BMD hip and lumbar scores and the amplitude and distal latency results of SSR ($p>0.05$) (Table 3).

Discussion

Studies have demonstrated the modulation of adrenergic receptors in the brain by estrogens (19,20). In postmenopausal OP, estrogen deficiency has been found to narrow the width of the thermoneutral zone by increasing brain norepinephrine. Consequently, disturbances in thermoregulation, such as hot flashes and excessive sweating, occur (10). Numerous tests assess the function of the autonomic nervous system, which include the evaluation of vasomotor and sudomotor symptoms. These tests encompass cardiovascular assessments, pupil reaction tests, lacrimal secretion tests, and SSR. In SSR studies, prolonged latency and low amplitude are considered indicative of sympathetic denervation (18,21).

Table 1. Demographic characteristics of the osteoporosis, osteopenic, and normal groups

	Osteoporotic (n=34)	Osteopenic (n=36)	Normal (n=31)	
	Mean±SD	Mean±SD	Mean±SD	p-value
Age, years	56.76±5.36	56.19±6.06	53.52± 4.21	0.036[1]
BMI, kg/m^2	26.42±3.99	26.57±3.54	28.68±4.24	0.040[1]
Menopause age, years	47.00±5.67	47.31±5.93	46.77±5.55	0.591[2]
Duration of menopause, years	9.76±6.57	8.89±6.32	6.74±6.63	0.055[2]

[1]One-way ANOVA, [2]Kruskal-Wallis test, BMI: Body mass index, SD: Standard deviation

Table 2. Sympathetic skin response data of upper and lower limbs in osteoporosis, osteopenic, and normal groups

		Osteoporotic (n=34)	Osteopenic (n=36)	Normal (n=31)	
		Mean±SD	Mean±SD	Mean±SD	p-value
Latency, s	Right hand	1.300±0.271	1.228±0.267	1.331±0.323	0.320[1]
	Left hand	1.306±0.298	1.269±0.295	1.331±0.332	0.690[1]
	Right foot	2.048±0.420	1.993±0.401	2.077±0.414	0.622[2]
	Left foot	2.047±0.384	2.034±0.383	2.080±0.441	0.722[2]
Amplitude, mV	Right hand	3.12±1.72	3.53±1.43	3.43±1.58	0.427[2]
	Left hand	3.12±1.59	3.36±1.30	3.47±1.95	0.790[2]
	Right foot	1.41±0.86	1.43±0.81	1.83±1.32	0.629[2]
	Left foot	1.30±0.86	1.40±0.87	1.88±1.40	0.246[2]

[1]One-way ANOVA, [2]Kruskal-Wallis test, s: Second, mV: Milivolt, SD: Standard deviation

Table 3. Results of the correlation of sympathetic skin response data of upper and lower limbs and BMD hip and spine scores

		BMD hip g/cm² (n=101)		BMD spine g/cm² (n=101)	
		r	p-value	r	p-value
Latency, s	Right hand	0.001	0.991[1]	-0.018	0.862[1]
	Left hand	0.032	0.749[1]	-0.020	0.846[1]
	Right foot	0.010	0.921[2]	0.069	0.494[2]
	Left foot	0.042	0.678[2]	0.071	0.483[2]
Amplitude, mv	Right hand	0.091	0.367[2]	0.132	0.187[2]
	Left hand	0.071	0.481[2]	0.084	0.406[2]
	Right foot	0.100	0.319[2]	0.088	0.382[2]
	Left foot	0.149	0.136[2]	0.172	0.085[2]

[1]Pearson correlation, [2]Spearman correlation, s: Second, mV: Milivolt, SD: Standard deviation, BMD: Bone mineral densitiy

The role of the sympathetic nervous system in OP has been demonstrated, yet its mechanism remains a subject of debate. Animal experiments and case reports have shown that sympathetic dysfunction can lead to OP (22,23). Roshanzamir et al. (24) suggested in their study involving 42 patients with electric burns and 50 control subjects that sympathetic nervous system dysfunction caused by electric burns is associated with OP. The results indicated that decreased BMD is correlated with prolonged latency and low amplitude in SSR. In a reverse perspective, animal experiments have suggested that blocking sympathetic nerve activity increases bone mass and prevents the progression of OP (25,26). Advanced age and low BMI are well-established risk factors for OP (27). In this study, the age of patients in the OP group was higher, and the BMI was lower.

Gast et al. (11) study involving 5600 female patients demonstrates that individuals with vasomotor symptoms exhibit higher sympathetic activation, and there is a correlation between hot flashes and a decrease in bone mass. Tosun et al. (28) identified prolonged latency and low amplitude in SSR examinations in the osteoporotic group compared to the control group in their study investigating autonomic dysfunction in postmenopausal OP. In the study conducted by Ashraf et al. (29) with 33 postmenopausal osteoporotic patients and 31 control subjects, significant latency delays were observed in both hand and foot SSR examinations in the osteoporotic group compared to the control group. Additionally, amplitudes were significantly lower in the osteoporotic group compared to the control group. In the osteoporotic group with more vasomotor symptoms, changes in SSR examinations were more pronounced. In this study, lower amplitude responses were observed in the osteoporotic group compared to the osteopenic and normal groups. Additionally, distal latency delays were shorter in the osteoporotic group compared to the control group. However, these differences were not statistically significant. In the study conducted by Ashraf et al. (29), vasomotor symptoms such as the frequency of hot flashes over 24 hours, the number of hot flashes per week, and the incidence of night sweats were comprehensively evaluated. Due to the heterogeneity in the distribution of vasomotor symptoms among the groups, their study found more significant changes in SSR in the osteoporotic group. In contrast, the study observed a homogeneous distribution of vasomotor symptoms across all groups. However, since the BMI parameter was higher in the control group, the thickness of the adipose tissue may have masked the conduction responses in the SSR evaluations (30,31).

Maser et al. (32) study, which investigated the relationship between autonomic nervous system function measurements in 66 type 1 diabetic patients and decreased BMD, demonstrated that measures of heart rate variability and circulating norepinephrine levels did not influence BMD in type 1 diabetes. Kado et al. (33) study, which evaluated the resting heart rate of 9702 women aged 65 and older, revealed an increased risk of hip, pelvic, and rib fractures in women with a resting heart rate exceeding 80 beats per minute. The cause of this association was attributed to the development of OP, linked to increased sympathetic activity and the consequent elevation of IL-6 production triggered by released catecholamines (34). As far as we know, there has been no identified study in the literature examining the correlation between BMD and SSR. In the present study, no significant correlation was observed between the BMD scores and SSR latencies and amplitudes for all patients. This suggests that BMD scores may not be directly associated with autonomic dysfunction.

The exclusion of systemic diseases and neurological diseases that may affect the autonomic nervous system and electrophysiological measurements to avoid possible confounders in the study design are among the strengths of the study.

Study Limitations

Among the limitations of this study is the lack of examination of other assessments commonly investigated in autonomic dysfunction, such as thermoregulation sweating tests, cardiovascular evaluations, and the assessment of the parasympathetic system. This limitation arises from the difficulty in performing detailed and comprehensive evaluations due to the high volume of patients examined simultaneously and constrained time resources in outpatient settings. Additionally,

the duration of patients' vasomotor symptoms was not investigated. Furthermore, low BMI, a risk factor for OP, was not evenly distributed in the demographic data.

Conclusion

In conclusion, this study did not identify a significant association between SSR which indicates autonomic dysfunction, and BMD scores in postmenopausal women. The limitations of the study, including the lack of assessment of other measures of autonomic function and the insufficiently detailed inquiry into vasomotor symptoms, may have influenced these results. To address these limitations and achieve a more comprehensive understanding, future research should include advanced tests evaluating various aspects of autonomic function and randomized studies with detailed assessments of vasomotor symptoms. Such studies could enhance our understanding of the potential relationships between autonomic dysfunction and bone health, and elucidate more complex interactions that were not captured in our study.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Health Sciences University of Türkiye Antalya Training and Research Hospital (date: 31.03.2022, decision number: 7/17).

Informed Consent: Written informed consent was obtained prior to the study from all subjects.

Acknowledgments

We express our gratitude to the referees for their invaluable comments and recommendations, which greatly contributed to the substantial improvement of our article.

Footnotes

Authorship Contributions

Concept: G.Ç., Ş.K.D., Design: G.Ç., M.B.F., Data Collection or Processing: G.Ç., M.H.S., Analysis or Interpretation: M.B.F., Ş.K.D., Literature Search: G.Ç., M.H.S., Writing: G.Ç., M.H.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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