

Sonographic Degree of Arterial Stiffness and Inflammatory Markers in Postmenopausal Osteoporosis

Postmenopozal Osteoporozda Arteriyel Sertlik ve Enflamatuvar Belirteçler

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Abstract

Objective: Arterial stiffness is used to diagnose and follow-up on many diseases. Although a specific interaction exists between osteoporosis and atherosclerosis, the correlation between arterial stiffness and osteoporosis has yet to be clearly established, and previous findings have been inconsistent. In this study, we aimed to determine whether a correlation exists between laboratory values employed in the diagnosis and follow-up of osteoporosis and arterial stiffness parameters.

Materials and Methods: The cases were categorized as osteopenia, osteoporosis and control groups according to dual X-ray absorptiometry findings. Arterial stiffness parameters (compliance, diastolic wall stress, elastic modulus, and distensibility) were assessed based on sonographic findings (intima-media thickness, systolic diameter, and diastolic diameter) for 108 postmenopausal women (46 with osteopenia, 38 with osteoporosis, and 24 controls). Laboratory findings employed in the diagnosis and follow-up of osteoporosis and inflammatory indicators were recorded. The groups were compared based on these parameters.

Results: The arterial stiffness parameters of intima-media thickness and compliance were significantly different between the patient and control groups ($p=0.003$ and $p=0.034$, respectively).

Conclusion: The incidence of arterial stiffness increased in patients with osteoporosis, as observed using ultrasonography-an easily accessible diagnostic tool. Inflammatory indicators increased in both osteoporosis and arterial stiffness cases.

Keywords: Osteoporosis, arterial stiffness, inflammation

Öz

Amaç: Arteriyel sertlik birçok hastalığın teşhisi ve takibinde kullanılır. Osteoporoz ve ateroskleroz arasında belirli bir etkileşim olmasına rağmen, arteriyel sertlik ile osteoporoz arasındaki korelasyon henüz net olarak belirlenmemiştir ve önceki bulgular değişkendir. Bu çalışmada, osteoporozun teşhisi ve takibinde kullanılan laboratuvar değerleri ile arteriyel sertlik parametreleri arasında bir korelasyon olup olmadığını belirlemeyi amaçladık.

Gereç ve Yöntem: Olgular, dual X-ray absorptiometri bulgularına göre osteopeni, osteoporoz ve kontrol grupları olarak kategorize edildi. Arteriyel sertlik parametreleri (uyum, diyastolik duvar gerilimi, elastik modül ve gerilebilirlik), 108 postmenopozal kadın (46 osteopeni, 38 osteoporoz ve 24 kontrol) için sonografik bulgulara (intima-media kalınlığı, sistolik çap ve diyastolik çap) dayanarak değerlendirildi. Osteoporozun teşhisi ve takibinde kullanılan laboratuvar bulguları ve enflamatuvar göstergeler kaydedildi. Gruplar bu parametrelere göre karşılaştırıldı.

Bulgular: İntima-media kalınlığı ve uyumun arteriyel sertlik parametreleri hasta ve kontrol grupları arasında önemli ölçüde farklıydı (sırasıyla $p=0,003$ ve $p=0,034$).

Sonuç: Osteoporozlu hastalarda arteriyel sertliğin görülme sıklığı, kolayca erişilebilen bir tanı aracı olan ultrasonografi kullanılarak gözlemlendiği gibi arttı. Hem osteoporoz hem de arteriyel sertlik olgularında enflamatuvar göstergeler artış gösterdi.

Anahtar kelimeler: Osteoporoz, arteriyel sertlik, enflamasyon

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Introduction

Osteoporosis is characterized by low bone mineral density and is a leading determinant of cardiovascular mortality, especially in postmenopausal women (1). Osteoporosis and atherosclerosis are the most common diseases that affect postmenopausal women. A certain degree of interaction exists between osteoporosis and vascular sclerosis; however, the underlying mechanisms remain unknown (2).

Arterial stiffness (AS) is an index of subclinical atherosclerosis. It is a dynamic characteristic, contingent upon the function and structure of the major arteries. Its clinical significance as a primary predictor of cardiovascular diseases has been well established in older adults and in various clinical conditions (rheumatoid arthritis, osteoarthritis, diabetes mellitus, vasculitis and hypertension) (3-5).

AS defines the viscoelastic properties of the arterial wall. The elasticity of large and medium arteries is critical for maintaining cardiovascular health. A decrease in flow pulsatility, associated with the elasticity of these arteries, ensures constant flow from the heart at the capillary level, maintaining steady perfusion in vital organs (6). A decrease in elasticity leads to a similar outcome at the periphery. However, it can also induce left ventricular hypertrophy through a decrease in pulse wave reflection (7). AS, which was emphasized as a pathological process in previous studies, develops against elasticity (8). Although a specific interaction exists between osteoporosis and atherosclerosis, the correlation between AS and osteoporosis has yet to be clearly established, and previous findings have been inconsistent. Pulse wave velocity (PWV) measurements have been used to demonstrate this correlation in previous studies (9,10).

Additionally, inflammatory processes have been described as risk factors for atherosclerosis and osteoporosis (11). A systematic review demonstrated the role of inflammation in the association between cardiovascular disease and osteoporosis (12). In addition to the correlation between osteoporosis and inflammatory markers, AS is associated with pro-inflammatory cytokines (13).

In the present study, we aimed to evaluate the correlations between the parameters of compliance, distensibility, diastolic wall stress and elastic modulus calculated using formulas based on sonographic carotid intima-media thickness (cIMT) and osteoporosis and inflammatory laboratory markers in postmenopausal osteoporosis patients.

Materials and Methods

Ethical Approval

This study was approved by the Medical Faculty Local Ethics Committee of a Kahramanmaraş Sütçü İmam University (2018/13; decision no: 14). This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all patients prior to the study.

Study Design

A total of 108 postmenopausal women aged 45-70 years who applied to the physical therapy and rehabilitation clinic with complaints of back pain, shortening of height, general body pain and posture disorder were included in the study. All women were experiencing natural menopause. The cases were categorized as osteopenia, osteoporosis and control groups according to dual X-ray absorptiometry findings. All patients underwent ultrasonography performed by an experienced radiologist using the same device. The group findings were analyzed.

Osteopenia and Osteoporosis Diagnosis

Bone mineral density was measured with Hologic QDR 4500 device (Bedford, MA). The measurements were conducted anteroposterior to the lumbar vertebrae (L1-L4) and proximal to the femur. The findings were categorized based on World Health Organization criteria into the following three groups (14): Group 1 (normal control group): T-scores >1 standard deviation, $n=24$; Group 2 (osteopenia group): T-scores range from -1 and -2.5 standard deviation, $n=46$; and Group 3 (osteoporosis group): T-scores <-2.5 standard deviation, $n=38$.

Exclusion Criteria

Patients with osteoporosis other than postmenopausal osteoporosis and those with concomitant diseases (diabetes mellitus, hypertension, metabolic disease, blood disease, acute/chronic infection, or inflammatory disease) were excluded. In addition, the study did not include patients receiving antiresorptive or bone-building drugs or vitamin D supplements. The control group cases had similar characteristics to the osteoporosis and osteopenia cases. In terms of the homogeneity of the control group, those with cardiovascular/hematological diseases, those with rheumatological diagnoses, and those with a history of bone metabolism disorders were not included in the study.

Carotid Doppler Measurement

The procedures were performed with women placed in the supine position. A high-resolution ultrasonography system (Aplio 400™, Toshiba Medical Systems Corporation, Tochigi, Japan) and broadband linear probe were applied. Blood vessel IMT and diastolic (DD) and systolic (SD) lumen diameters were measured after the probe was inserted 2 cm anterior to the bifurcation of the left carotid artery. Screen magnification was performed to improve accuracy in the B-mode IMT measurement. Measurements were conducted after at least three similar waveforms were observed without artifacts in SD and DD measurements of the M-mode images. Pulse pressure (systolic pressure, diastolic pressure, ΔP) was measured with an automatic sphygmomanometer (OCR Vitagnost 2015, MARS, Taiwan). The AS parameters of the vessel were calculated using the following formulas (15).

- Cross-sectional compliance = $(\pi \cdot [SD2-DD2]) / (4 \cdot \Delta P)$
- Cross-sectional distensibility = $(SD2-DD2) / (DD2 \cdot \Delta P)$
- Diastolic wall stress = $(DD / [2 \cdot IMT]) \cdot ([\text{systolic pressure} + SD] / 2)$
- Elastic modulus = $(3 / [1 + \{\text{cross-sectional area of lumen} / \text{cross-sectional area of wall}\}]) / \text{cross-sectional distensibility}$.

Statistical Analysis

Values are evaluated as mean + standard deviation. Analysis of variance was applied for group comparisons. Tukey's honestly significant difference was employed for intragroup comparisons. Beta coefficients with a 95% confidence interval were used in the analyses. Statistical tests were conducted using Statistical Package for Social Sciences (version 22.0; IBM Statistics for Windows version 17, IBM Corporation, Armonk, NY), and the significance level was set at $p < 0.05$.

Results

No statistically significant difference was observed between the control group cases and the osteoporosis and osteopenia cases in terms of age, body mass index (BMI), systolic and diastolic blood pressure values (Table 1).

BMI and mean age of the cases are presented in Table 1. Vitamin D levels were significantly lower in the osteoporosis group than in the control group ($p = 0.029$). Low-density lipoprotein cholesterol levels were also lower in the osteoporosis group than in the

control group ($p = 0.025$). Data for other biochemical parameters are presented in Table 2.

Platelet lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) were significantly higher in the osteoporosis group than in the control group ($p = 0.007$ and $p = 0.016$, respectively). The comparison of inflammatory values between the groups is presented in Table 3. The women were categorized based on weight as follows: Normal weight (group 1, $n = 63$; BMI ≤ 29.9 kg/m²) and obese (group 2, $n = 45$; BMI ≥ 30 kg/m²). The correlation between BMI and vascular morphology indicators was used to analyze between-group differences. Statistically significant differences were observed between the groups based on cIMT ($p = 0.024$, $p = 0.150$, $p = 0.143$, and $p = 0.273$, respectively; Table 4). Analysis of vascular morphology based on age revealed that vascular morphological properties were negatively affected by advanced age, especially in the osteoporosis group (all $p < 0.01$). Although vascular morphology was negatively affected by age in the control group, no statistical difference was observed (all $p > 0.05$; Table 5). A statistically negative correlation was observed for NLR and all AS parameters (all $p < 0.01$).

Evaluation of factors that affected vascular morphological parameters with correlation analysis revealed a positive correlation between cIMT and osteoporosis ($r = 0.316$, $p < 0.001$) and increase in BMI ($r = 0.329$, $p < 0.001$) and NLR ($r = 0.282$, $p < 0.003$). However, a negative correlation was observed between cIMT and lymphocyte ratio ($r = -0.264$, $p < 0.006$; Table 5).

Table 1. Baseline characteristics of the study participants

Characteristic	Control (n=24)	Osteopenia (n=46)	Osteoporosis (n=38)	p-value
Age (years)	55.75±6.63	60.04±8.65	60.50±8.04	0.056
BMI (kg/m ²)	32.52±3.27	30.90±4.81	29.66±4.26	0.043
SBP (mmHg)	123.75±16.10	126.95±21.01	125.3±24.59	0.827
DBP (mmHg)	77.50±4.42	77.60±10.04	79.47±11.31	0.619

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 2. Comparison of biochemical and hormonal parameters between the study groups

Characteristic	Control (n=24)	Osteopenia (n=46)	Osteoporosis (n=38)	p-value
Vitamin D (mg/dL)	26.82±31.32	18.82±13.12	12.53±7.63	0.029
Calcium (mg/dL)	9.6±0.37	9.54±0.37	9.45±0.50	0.213
Total cholesterol (mg/dL)	241.60±10.91	214.00±32.92	214.54±19.98	0.040
HDL-cholesterol (mg/dL)	47.00±9.48	48.88±9.00	48.30±7.74	0.837
Triglycerides (mg/dL)	128.37±15.37	129.78±28.43	117.93±17.22	0.179
LDL-cholesterol (mg/dL)	206.00±18.47	179.28±19.27	181.75±30.38	0.035
ALP	266.66±157.40	179.70±74.30	148.21±81.13	0.011
TSH	86.50±32.17	83.62±23.86	73.32±27.66	0.206
FT4	3.50±4.43	1.70±1.53	1.19±0.99	0.003
Vitamin B12	1.20±0.10	1.17±0.17	1.14±0.29	0.745
Ferritin	446.60±143.39	461.83±388.54	394.40±155.90	0.618

HDL: High-density lipoprotein, LDL: Low-density lipoprotein, ALP: Alkaline phosphatase, TSH: Thyroid-stimulating hormone, FT4: Free thyroxine, ANOVA: Analysis of Variance, HSD: Honestly significant difference

Table 3. Comparison of inflammatory and hematological parameters between the study groups

Characteristic	Control (n=24)	Osteopenia (n=46)	Osteoporosis (n=38)	p-value
CRP	5.41±2.33	5.99±5.65	6.45±4.82	0.770
Neutrophil percentage	51.71±6.28	57.14±9.07	58.14±11.01	0.025
Lymphocyte percentage	37.66±6.49	31.94±7.20	30.63±8.39	0.002
Platelet (K/ μ L)	262.62±42.17	262.00±39.95	276.21±58.19	0.356
NLR	1.24±0.38	2.00±1.06	2.20±1.21	0.016
PLR	7.07±1.15	8.83±3.33	10.08±4.68	0.007

CRP: C-reactive protein, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio

Table 4. Comparison of vascular stiffness parameters

Characteristic	Control (n=24)	Osteopenia (n=46)	Osteoporosis (n=38)	p-value
Intima-media thickness (mm)	0.623±0.089	0.649±0.125	0.725±0.142	0.003
Compliance	0.058±0.037	0.071±0.045	0.116±0.156	0.034
Elastic modulus (N/m ²)	746.42±505.28	571.72±514.21	502.80±264.00	0.048
Distensibility (mmHg $\times 10^3$)	0.0020±0.001	0.0026±0.002	0.0037±0.004	0.028

ANOVA: Analysis of Variance, HSD: Honestly significant difference

Table 5. Evaluation of factors associated with vascular morphological structure

	Intima-media thickness (mm)		Compliance		Distensibility (mmHg $\times 10^3$)		Elastic modulus (N/m ²)	
	Ratio	p-value	Ratio	p-value	Ratio	p-value	Ratio	p-value
Osteoporosis	0.316	0.001	0.185	0.063	0.181	0.068	-0.163	0.091
Age	0.649	0.001	0.385	0.001	0.385	0.001	-0.425	0.001
BMI	0.329	0.001	0.220	0.026	0.256	0.009	-0.240	0.012
SBP	0.438	0.001	0.286	0.004	0.374	0.001	-0.386	0.001
Ca	0.030	0.755	0.116	0.245	0.234	0.018	-0.184	0.050
Vitamin D	0.120	0.217	0.182	0.068	0.255	0.010	-0.201	0.037
HDL (mg/dL)	-0.039	0.777	0.298	0.027	0.294	0.029	0.214	0.117
LDL (mg/dL)	0.418	0.002	0.042	0.768	0.106	0.449	-0.304	0.002
Neu %	0.268	0.006	0.290	0.003	0.359	0.001	-0.172	0.189
Lymp %	-0.264	0.006	-0.304	0.002	-0.306	0.002	0.267	0.006
NLR	0.282	0.003	0.304	0.002	0.336	0.001	-0.292	0.002

Ca: Calcium, BMI: Body mass index, SBP: Systolic blood pressure (mmHg), HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Neu %: Neutrophil percentage, Lymp %: Lymphocyte percentage, NLR: Neutrophil to lymphocyte ratio

Discussion

The primary findings of our study were as follows: Vitamin D and low-density lipoprotein cholesterol levels were significantly lower in the osteoporosis group than in the control group, as expected; inflammatory markers (NLR and PLR) were significantly higher in the osteoporosis group than in the control group; AS markers (IMT and compliance) were significantly higher in the osteoporosis group than in the control group; among AS markers, only IMT correlated with obesity; all AS markers declined with age; and all AS markers were negatively affected by the increase in NLR.

Empirical studies have highlighted several factors affecting disease development in bones and arteries (16). NLR and PLR are indicators of systemic inflammatory response (17). Inflammatory markers modulate bone formation and resorption by activating osteoclasts that surround cytokines (18). Thus, a systemic inflammatory process may be a mechanism shared by the development of low bone mass and atherosclerosis (16). The high incidence of postmenopausal osteoporosis accompanied by several inflammatory diseases (Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, and systemic lupus erythematosus) reported in the literature reveals a correlation between chronic inflammation and

postmenopausal osteoporosis (19). Furthermore, a systematic review highlighted the role of inflammation in the correlation between cardiovascular disease and osteoporosis (12). Owing to the correlation between osteoporosis and inflammatory markers, AS is also associated with proinflammatory cytokines (13). The present study demonstrates that the data were significant and align with the data results reported in the literature within the same patient group.

The prevalence of osteoporosis increases with age (20). Atherosclerosis also progresses with age, and its risk increases significantly after menopause in women (21). The degree of vascular calcification is significantly associated with the changes in bone density, suggesting that vascular sclerosis and low bone mass are associated with pathological conditions (22). The data reported in the literature were significant and aligned with the observations made within the same patient group.

AS measurement is a non-invasive procedure, with two types of measurement techniques. The qualitative technique estimates stiffness using arterial waveform analysis and diameter measurements. The quantitative technique estimates stiffness using parameters such as compliance, diastolic wall stress, distensibility, and elastic modulus based on sonographic cIMT calculations. Compliance is the absolute change in diameter with an increase in pressure. Diastolic wall stress indicates the force on the vessel wall area during diastole. Distensibility is the proportional change in diameter due to an increase in pressure. The elastic modulus describes the characteristics of the wall, independent of the arterial architecture. IMT is a structural property, while compliance, distensibility, diastolic wall stress, elastic modulus, and PWV are functional properties (23). PWV is a broad regional indicator of AS along a particular arterial length. Compliance, diastolic wall stress, distensibility, and elastic modulus are local AS markers in more restricted areas (24).

An increase in AS precedes atherosclerosis and is considered an early marker of systemic atherosclerosis. AS is an independent guiding guide of morbidity and mortality in cardiovascular disease. An association between an increase in AS and cardiovascular events has been demonstrated in high-risk groups (e.g., those with chronic kidney disease or hypertension) and the general population without a diagnosis (25). Mangiafico et al. (26) reported that AS measured using artificial intelligence increased in postmenopausal osteoporotic women. In the present study, we measured AS based on parameters formulated using sonographic IMT and demonstrated a correlation between AS and osteoporosis.

Osteoporosis and cardiovascular diseases aggravate with age and share common risk factors. Although the interaction between osteoporosis and vascular sclerosis exists, the underlying mechanisms remain unknown. Vascular calcification is a well-established mechanism (2). Arterial wall calcification is expected to increase AS without affecting subclinical measures of atherosclerosis, including cIMT. Bone mass loss in postmenopausal women and patients undergoing hemodialysis is associated with

high AS (26). Furthermore, osteoporosis and atherosclerosis share certain risk factors such as hypertension, smoking, and a sedentary lifestyle (27). Estrogen could be a critical factor in the association between bone mineral loss and AS. Its receptors have been found in osteoblasts, osteoclasts, and the vasculature. Its deficiency is a risk factor for cardiovascular diseases and bone loss, with bone mass decreasing with age, independent of sex. Specifically women are at higher risk, especially after menopause when bone mass declines rapidly owing to decreased estrogen levels (28). Cross-sectional studies have demonstrated that estrogen deficiency during menopause is associated with increased AS (29). The present study demonstrated this correlation in postmenopausal women, a potentially estrogen-deficient group.

Study Limitations

The main limitations of the present study include the small sample size and lack of dietary calcium and vitamin D content analysis. Furthermore, although the patient group included postmenopausal women, the lack of estrogen measurements may have limited specific findings. In addition, another important factor that could affect the relationship between osteoporosis and AS is estrogen levels (30). The fact that estrogen levels were not included in our study may have been a limiting factor in understanding the relationship between osteoporosis and AS. In further studies investigating the relationship between osteoporosis and AS, evaluating estrogen levels and related hormonal parameters will contribute to the literature.

Conclusion

With advancing age, AS is an essential indicator of cardiovascular disease in postmenopausal women with osteoporosis. AS can be identified using ultrasonography, which is an inexpensive and simple method. Inflammatory parameters may serve as indicators of both osteoporosis and AS.

Ethics

Ethics Committee Approval: This study was approved by the Medical Faculty Local Ethics Committee of a Kahramanmaraş Sütçü İmam University (2018/13; decision no: 14). This study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all patients prior to the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.B., K.D., Concept: E.B., Design: E.B., K.D., Data Collection or Processing: E.B., Analysis or Interpretation: E.B., K.D., Literature Search: E.B., K.D., Writing: E.B.

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