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The Relationship Between Bone Mineral Density and Aortic Valve – Mitral Valve Calcification in Postmenopausal Women

Postmenopozal Kadınlarda Kemik Mineral Yoğunluğu ile Aort Kapak- Mitral Kapak Kalsifikasyonu Arasındaki İlişki

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ÖZET

AMAÇ: Osteoporoz ve kalp kapağı kalsifikasyonu (KKK), yaşlanan nüfusta ciddi morbidite ve mortaliteye neden olan yaygın hastalıklardır. Çalışmamız, menopoz sonrası kadınlarda osteoporoz ve kalp kapağı kalsifikasyonu arasındaki ilişkiyi araştırmak üzere planlandı.

GEREÇ VE YÖNTEM: Son bir yıl içinde kemik mineral yoğunluğu (KMY) ve ekokardiyografi (EKO) yapılan 50-75 yaş arası menopoz sonrası hastalar çalışmaya dahil edildi ve lomber omurga (LO) ve femur boynu (FB) KMY ölçümleri ile EKO ölçümleri değerlendirildi. KMY ölçümleri normal, osteopeni ve osteoporoz (OO) olarak gruplandırıldı. KKK olan ve olmayan hastalar osteopeni ve osteoporoz varlığına göre karşılaştırıldı.

BULGULAR: Çalışmaya toplam 77 menopoz sonrası kadın dahil edildi. KKK bunların 38'inde (%49,4) tespit edildi. Sadece aort kapak kalsifikasyonu (AKK) 33 (43%) hastada, sadece mitral kapak kalsifikasyonu (MKK) 20 (26%) hastada ve hem AKK hem de MKK 15 (19%) hastada tespit edildi. Otuz üç AKK'lı hastadan 25'inde (76%) LO OO ve 24'ünde (73%) FB OO vardı. MKK'lı 20 hastadan 15'inin (75%) LO OO'su ve 15'inin (75%) FB OO'su vardı.

SONUÇ: Sonuç olarak, düşük kemik kütlesinin menopoz sonrası kadınlarda KKK üzerinde bağımsız ve olumsuz bir etkisi olduğunu bulduk. Osteopeni veya osteoporozu olan menopoz sonrası kadınların KKK'nın erken teşhisi için uyarılması ve yönlendirilmesi gerektiğini sonucuna vardık.

Anahtar Kelimeler: kardiyovasküler risk faktörleri, koruyucu kardiyoloji, kapak hastalıkları, kemik mineral yoğunluğu, postmenopozal kadın

ABSTRACT

OBJECTIVE: Osteoporosis and heart valve calcification (HVC) are common diseases that cause serious morbidity and mortality in the aging population. Our study was planned to investigate the relationship between osteoporosis and HVC in postmenopausal women.

MATERIALS AND METHODS: Postmenopausal patients aged 50-75 years who had bone mineral density (BMD) and echocardiography (ECO) within the last year were included in the study and lumbar spine (LS) and femoral neck (FN) BMD measurements and ECO measurements were evaluated. BMD measurements were grouped as normal, osteopenia and osteoporosis. Patients with and without HVC were compared according to the presence of osteopenia and osteoporosis.

RESULTS: A total of 77 postmenopausal women were included in the study. HVC was detected in 38 (49.4%) of them. Only aortic valve calcification (AVC) was detected in 33 (43%) patients, only mitral valve calcification (MVC) was detected in 20 (26%) patients and both AVC and MVC were detected in 15 (19%) patients. Of the 33 patients with AVC, 25 (76%) had LS osteopenia/osteoporosis (OO) and 24 (73%) had FN OO. Of the 20 patients with MVC, 15 (75%) had LS OO and 15 (75%) had FN OO.

CONCLUSION: In conclusion, we found that low bone mass has an independent and negative effect on HVC in postmenopausal women. We concluded that postmenopausal women with osteopenia or osteoporosis should be warned and referred for early diagnosis of HVC.

Keywords: cardiovascular risk factors, preventive cardiology, valve disease, bone mineral density, postmenopausal women

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INTRODUCTION

Osteoporosis and heart valve calcification (HVC) are prevalent conditions that result in considerable morbidity and mortality among the elderly population. Osteoporosis is a skeletal disorder marked by reduced bone mineral density (BMD), degradation of bone architecture, and heightened incidence of fractures.[1] Menopause, defined as the natural cessation of the menstrual cycle, is the most important factor in BMD decrease and is measured standardly using dual-energy X-ray absorptiometry (DEXA).[2,3] Mitral valve calcification (MVC) is a condition characterized by calcium accumulation in the mitral valve or annulus.[4] It is one of the most common pathologies seen in cardiac imaging techniques. Although there are findings that it begins with endothelial damage and lipid infiltration, its pathophysiology is not fully understood.[5,6] While treatment cannot be predicted in the initial and progressive stages of the process, treatment is attempted with surgical or percutaneous methods in the advanced stages.[7-9] Aortic valve calcification (AVC) has been the subject of many studies because it is frequently seen together with coronary artery diseases and hypertension.[10] It has been shown that it has pathophysiological similarities with the development of MVC; in addition, mechanical stress is thought to initiate inflammation.[7,11] Growing data indicates that HVC is negatively correlated with BMD, independent of age and other clinical risk factors.[12] Histopathological analyses indicate that valve and annular calcification display features akin to bone development and remodelling. This indicates that this form of ectopic calcification is associated with bone metabolism and control.[5,6,13] Numerous population-based investigations have demonstrated the correlation between bone health and extra skeletal calcification.[12,14] Reduced (BMD) has been correlated with an increased incidence of calcification in the mitral and aortic valves.[15-18] In a previous study, BMD T-score was shown to be an independent variable for HVC in women, but such a connection could not be detected in men.[18] There are studies showing that women with low bone mass are at greater risk for the presence of cardiovascular diseases (mostly abdominal aortic calcification or coronary heart disease).[19-21] However, the number of studies on valve calcification is few.

Accelerated BMD loss in the postmenopausal period is well known. To our knowledge, there is no study examining the relationship between BMD and aortic/mitral valve calcification using DEXA and electrocardiography (ECO), focusing on postmenopausal women. In this context, we aimed to investigate the relationship between BMD and valve calcifications in postmenopausal women

MATERIAL & METHODS

This retrospective study was conducted at Medical Park Hospital between September 2023 and September 2024. The study protocol was approved by University of Mudanya Clinical Research Ethics Committee (No.2024-04). All procedures were carried out in accordance with the principles of the Helsinki Declaration of the World Medical Association. The records of postmenopausal female patients between the ages of 50 and 75 who were followed up in cardiology and physical medicine and rehabilitation (PMR) clinics were scanned. Among patients who had BMD and ECO scanned in the last year, those with rheumatic heart disease, hypertrophic obstructive cardiomyopathy, previous myocardial infarction, oncological diseases, diseases affecting bone and mineral metabolism (hyperparathyroidism, significant thyroid dysfunction, chronic renal failure, or adrenal insufficiency), and those who had previously received osteoporosis treatment were excluded from the study. Seventy-seven patients who met the conditions were included in the study. Clinical and demographic characteristics including age, gender, body mass index, hypertension, diabetes, and hypercholesterolemia were recorded.

BMD (g/cm²) measures of the lumbar spine (LS) (L1–L4) and femoral neck (FN) were evaluated using DEXA (QDR-4500W; Hologic, Bedford, MA, USA). The anteroposterior spine measurement was conducted from the L1 to L4 vertebrae. Patients were categorized based on their T score values as having osteoporosis, osteopenia, or being normal, in accordance with the World Health Organization's diagnostic criteria for osteoporosis established in 1994.[22] The T-score reflects the disparity between the patient's BMD and the average BMD of healthy young adults, adjusted for sex and ethnicity. Osteoporosis was diagnosed when the individual T-score value was ≤-2.5 at the spine or hip; a T-score between -2.5 and -1 was defined as osteopenia; and a T-score ≥-1 was considered normal or healthy.

ECO measurements of the patients were performed routinely in the cardiology outpatient clinic by the cardiologist at rest in the left decubitus position, with parasternal short and long axis images and two-

dimensional imaging in the apical four-chamber and two-chamber positions.[23] The necessary two-dimensional, M-mode, colour doppler, PW doppler, and TDI doppler images from the parasternal and apical windows were taken and measured using a Philips, affinity 50W, Germany device, 2-5 MHz, specific probe for field studies. All measurements were repeated at least three or four times and averaged. ECO measurements are performed in the cardiology outpatient clinic in accordance with the recommendations of the American Society of Echocardiography.[24] All Doppler echocardiography and Tissue Doppler Imaging Echocardiography measurements were made during normal respiration. In the apical four-chamber view, the structure and calcification of the aortic and mitral valves, mitral valve, aortic and tricuspid valve insufficiencies were evaluated using colour doppler, and maximum and average gradients at the aortic and mitral valve levels were evaluated using continuous wave doppler.[20] Echocardiographically, the degree of AVC was determined according to Rosenhek scoring. AVC was graded as grade 1 (no calcification detected), grade 2 (mild calcification, small isolated spots) grade 3 (moderate calcification, multiple large puncta), and grade 4 (severe calcification, widespread calcification involving all valves). MVC score was evaluated as presence or absence of calcification. The relationship between valve lesions in patients with normal BMD and those with osteopenia or osteoporosis was compared and evaluated.

The patients were divided into two groups: those without valve calcification (group 1) and those with it (group 2). BMD measurements were grouped as normal, osteopenia, and osteoporosis. Group 1 and group 2 were compared using statistical methods according to the presence of osteopenia and osteoporosis.

Statistical Analysis: The data collected in the study were statistically analysed using IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). The sample size for this study was calculated with a power of at least 80% for each variable and a Type I error rate of 5%. The Shapiro-Wilk test (n<50) and Skewness-Kurtosis tests were employed to assess the normality of the continuous measurements in the study. Given the consistent distribution of the values, parametric tests were utilized. Descriptive statistics for the study variables, presented as mean, standard deviation, sample size (n), and percentage (%). The "Independent T-test" was employed to compare measures based on "categorical factors". The "Chi-square test" was employed to ascertain the correlations among categorical variables. Pearson correlation coefficients were computed to ascertain the link between measurements. The level of statistical significance was $p < 0,05$.

RESULTS

A total of 77 postmenopausal female patients were included in the study. HVC was detected in 38 of them (49,4%). The basic characteristics of the patients are shown in Table 1 according to the presence or absence of HVC. L1-4 T score mean values and vitamin D levels were found to be statistically significantly ($p<0,05$) lower in patients with HVC. The presence of hypertension was higher in patients with HVC had a higher prevalence of hypertension, which was statistically significant. There was no difference between the groups in terms of other characteristics ($p>0,05$).

Table.1. *Characteristics of patients according to the presence or absence of HVC*

	Grup 1 (n=39)	**Grup 2 (n=38)**	***p***
Age, mean ± sd	61,02±8,99	61.72±8,89	>0,05
Body mass index, mean ± sd	26,72±4,98	28,04±4,53	>0,05
Hypertension, n (%)	17(%43,6)	28(%73,7)	<0,05*
Diabetes, n (%)	6(%15,4)	13(%34,2)	>0,05
Vitamin D level, mean± sd	29,04±9,17	20,58±11,61	<0,05*
Smoking, n (%)	19 (%49)	18 (%47)	>0,05
Hypercholesterolemia, n (%)	20 (%51)	23 (%61)	>0,05
T score L1-4, mean ± sd	-1,14±1,20	-1,73±1,18	<0,05*
T score femoral neck, mean ± sd	-1,28±0,78	-1,45±0,83	<0,05

sd: standard deviation

The distribution of patients in Group 2 according to the affected heart valve is given in Table 2. Only AVC was detected in 33 patients, only MVC was detected in 20 patients, and both AVC and MVC were detected in 15 patients. LS osteopenia/osteoporosis (OO) was detected in 25 (76%) of 33 patients with AVC, and FN OO was detected in 24 (73%). LS OO was detected in 15 (75%) of 20 MVC patients, and FN OO was detected in 15 (75%) (Table 3).

Table 2. *Distribution of patients according to the presence of HVC*

	(n=38, %)
MVC	20 (26,0%)
MVC/AVC	15(32,5%)
AVC	33 (42,9%)
AVC Grade 1	0 (0,0%)
AVC Grade 2	31 (40,3%)
AVC Grade 3	2 (2,6%)
AVC Grade4	0 (0,0%)

HVC: heart valve calcification MVC: mitral valve calcification AVC: aortic valve calcification

Table 3. *Comparison of patients with AVC and MVC in terms of the presence of OO)*

	AVC (n=33) n (%)	MVC (n=20) n (%)	*p*
LS -Normal -OO	 8(24) 25(76)	 5(25) 15(75)	<0,05*
FN -Normal -OO	 9(27) 24(73)	 5(25) 15(75)	<0,05*

AVC: aortic valve calcification MVC: mitral valve calcification LS: lumbar spine FN: femoral neck OO: osteopenia/osteoporosis

Table 4. *Distribution of patients' osteopenic and osteoporotic BMD values according to HVC*

	Grup 1 (n=39) (n, %)	Grup 2 (n=38) (n, %)	*p*
LS T-score			
osteopenia	22 (59,5)	15 (40,5)	*<0,05**
osteoporosis	4 (22,2)	14 (77,8)	*<0,05**
FN T-score			
osteopenia	28- (57,1)	21- (42,9)	*<0,05**
osteoporosis	0- (0)	6- (100,0)	*<0,05**

LS: lumbar spine FN: femoral neck HVC: heart valve calcification

Table 5. *AVC and MVC distribution in osteopenic and osteoporotic patients*

	Total (n=77) n (%)	HVC + n (%) n=38	AVC + n (%) n=33	MVC + n (%) n=20
LS T-score OO	55(%71)	29(%53) /55	25(%86) /29	16(%55) /29
FN T-score OO	54(%70)	27(%50) /54	27 (%100) /27	15(%56) /27

HVC: heart valve calcification AVC: aortic valve calcification MVC: mitral valve calcification LS: lumbar spine FN: femoral neck

The distribution of patients according to HVC status is shown in Table 4. There is more osteopenia in the non-HVC group than in the HVC group. In the osteoporotic group, the number of patients with HVC was found to be statistically significantly higher than those without HVC. There was no statistically significant difference in HVC in patients with normal FN BMD measurements. In the osteopenic patient group, the number of patients without HVC was significantly higher than those with HVC. In the osteoporotic group, the number of patients with HVC was found to be statistically significantly higher than those without HVC.

LS and FN T-score values in 55 of 77 patients (71%) were osteopenic or osteoporotic. In the LS OO group, HVC was detected in 29 of 55 patients (52%). In the FN OO group, HVC was detected in 27 of 54 patients (50%). AVC and MVC were detected in 25 of 29 patients in the LS group, and AVC and MVC were detected in 16 of 27 patients in the FN group (Table 5).

DISCUSSION

In our study, we found that the mean values of BMD LS T score and FN T score were significantly lower in patients with HVC. We determined that the frequency of CVH increases as the severity of osteoporosis increases. Although many epidemiological and clinical studies have been reported showing a significant relationship between low BMD values and cardiovascular calcification (coronary artery, abdominal aorta), there are few studies on the relationship between BMD values and valve calcification.[10,11,13]

MVC is a condition characterized by calcium accumulation in the mitral valve, which controls the blood flow between the left atrium and left ventricle in the heart.[5] Although there are few publications indicating that it is more common in women in the postmenopausal period, the

pathophysiology of this relationship is not fully understood.[19,25] According to the literature, its prevalence varies between approximately 8% and 15%.[25] In our study, we found the prevalence of MVC to be 26%. This high result seems to be related to the specific patient population we selected, considering that MVC is more common in women and especially in the postmenopausal period.

Similarly, fibrocalcific remodelling and thickening begin in the aortic valve over time, and severe valve calcification occurs with impaired valve movement over time, leading to serious stenosis in cardiac output.[24] The prevalence of calcific aortic stenosis increases with age, and the prevalence varies between 9% and 42%.[25] Similarly, in our study, this rate was found to be 42.9%. We could not find many publications discussing the effects of bone metabolism changes on AVC in postmenopausal women. However, in our study, we found that AVC was higher in postmenopausal women who developed osteoporosis.

It has been suggested that AVC is also affected by cardiovascular disease risk factors in the postmenopausal period, unlike men and older patients.[18] Given that estrogen is a recognized factor in elucidating the pathophysiology of osteoporosis and cardiovascular disease, its insufficiency may also serve as a plausible explanation for these associations.[17] Moreover, estrogen receptor polymorphism, linked to diminished bone mass, has been documented in several clinical trials. This shows that genetic factors as well as estrogenic factors play a role.[26] Endothelial damage occurring in areas under mechanical stress may lead to an inflammatory response infiltrated by macrophages and T cells and lymphocytic infiltration, leading to myofibroblasts and preosteoblasts producing bone morphogenetic proteins.[5] Transforming growth factor beta1 (TGF-β1) is a double-acting factor that is abundant in bone and promotes bone formation while preventing bone destruction.[27] TGF-β1, released during the destructive activity of osteoclasts, can push bone cells into programmed cell death (apoptosis), contributing to a decrease in bone mass and, consequently, to the development of osteoporosis.[27] At the same time, TGF-β1 plays a critical role in the differentiation of valvular interstitial cells into the osteoblast phenotype. This may signal the beginning of the valve calcification process.[28] While TGF-β1, which plays an important regulatory role on the differentiation potential of mesenchymal cells, promotes cell proliferation at low concentrations with its concentration-dependent bimodal effect, these effects are not observed at high concentrations.[29] In this context, the effects of TGF-β1 on both bone tissue and valvular cells suggest that it is an important factor in calcification processes. Arıcı A et al. In a study conducted by et al., it was found that TGF-β1 serum levels in osteoporotic postmenopausal women were higher than in non-osteoporotic women.[29] We thought that this might be one of the possible reasons for the higher incidence of MVC in postmenopausal women. According to another hypothesis, Fetuin-A is a calcium-binding protein found in plasma both in free form and in complex with matrix gla protein (MGP). Fetuin-A, which plays an important role in the inhibition of vascular calcification, prevents calcium accumulation in vascular tissues by binding calcium ions and calcium crystals in the circulation.[30] Recent studies have shown that there is a connection between low serum fetuin-A levels and aortic valve calcification.[31,32] Studies revealing the relationship between postmenopausal osteoporosis and fetuin-A deficiency have revealed findings that, when evaluated in terms of bone mineralization, it can be used as a biochemical parameter in the diagnosis and treatment of postmenopausal osteoporosis.[33]

Vitamin D, a recognized element, also beneficially influences calcium metabolism and bone density.[34] Vitamin D mitigates myocardial ischemia-reperfusion injury and reactive oxygen species, while exerting beneficial effects on inflammation and thrombosis.[35,36] Moreover, reduced levels of 25(OH)D facilitate atherosclerosis, persistent inflammation, endothelial impairment, and arterial calcification.[37] Various studies demonstrate the impact of vitamin D insufficiency on the inflammatory process, a mechanism contributing to atherosclerosis.[34,38] Our findings revealed that vitamin D levels were markedly deficient in the patient cohort exhibiting valve calcification. We thought that low vitamin D levels might influence the inflammation process in the valves through a similar mechanism.

We assume that osteoporosis will increase much more, especially with longer life spans, and that it will also be effective in increasing the prevalence of calcific heart valve diseases. For this reason, we think that women who have gone through menopause should have BMD measured at regular intervals, which is a simple and inexpensive method, and taking early precautions against possible

osteoporosis would be beneficial in preventing possible calcific valve diseases.

Limitations of our study; It is cross-sectional, the number of patients is small, and estrogen levels are not measured.

CONCLUSION

In conclusion, we found that in postmenopausal women, low BMD has an independent and negative impact on CVH. We reasoned that there may be a common pathophysiological mechanism for low BMD and CVH. We concluded that postmenopausal women with osteopenia or osteoporosis should be warned and guided for the early diagnosis of CVH.

Etik: Bu çalışmanın etik kurulu alınmıştır.

Ethics committee approval had been taken.

Yazar katkı durumu; Çalışmanın konsepti; SK, HG, AD, MCB, dizaynı; SK, HG, AD, MCB, Literatür taraması; SK, HG, AD, MCB, verilerin toplanması ve işlenmesi; SK, HG, AD, MCB, istatistik; SK, HG, AD, MCB, yazım aşaması; SK, HG, AD, MCB.

Author contribution status; The concept of the study; SK, HG, AD, MCB, design; SK, HG, AD, MCB, literature review; SK, HG, AD, MCB, collecting and processing data; SK, HG, AD, MCB, statistics; SK, HG, AD, MCB, writing phase; SK, HG, AD, MCB.

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REFERENCES

1. Massera D, Xu S, Bartz TM, Bortnick AE, Ix JH, Chonchol M, et al. Relationship of bone mineral density with valvular and annular calcification in community-dwelling older people: The Cardiovascular Health Study. Archives of osteoporosis. 2017;12:1-12.

2. Kanis J, Glüer C. for the Committee of Scientific Advisors, International Osteoporosis Foundation. An update on the diagnosis and assessment of osteoporosis with densitometry. Osteoporos Int. 2000;11(3):192-202.

3. Rachner TD, Khosla S, Hofbauer LC. Osteoporosis: now and the future. The Lancet. 2011;377(9773):1276-87.

4. Uchimuro T, Fukui T, Shimizu A, Takanashi S. Mitral valve surgery in patients with severe mitral annular calcification. The Annals of Thoracic Surgery. 2016;101(3):889-95.

5. Mohler III ER, Gannon F, Reynolds C, Zimmerman R, Keane MG, Kaplan FS. Bone formation and inflammation in cardiac valves. Circulation. 2001;103(11):1522-8.

6. Arounlangsy P, Sawabe M, Izumiyama N, Koike M. Histopathogenesis of early-stage mitral annular calcification. Journal of medical and dental sciences. 2004;51(1):35-44.

7. Rajamannan NM, Evans FJ, Aikawa E, Grande-Allen KJ, Demer LL, Heistad DD, et al. Calcific aortic valve disease: not simply a degenerative process a review and agenda for research from the National Heart and Lung and Blood Institute Aortic Stenosis Working Group. Circulation. 2011;124(16):1783.

8. Labovitz AJ, Nelson JG, Windhorst DM, Kennedy HL, Williams GA. Frequency of mitral valve dysfunction from mitral anular calcium as detected by Doppler echocardiography. The American journal of cardiology. 1985;55(1):133-7.

9. Sud K, Agarwal S, Parashar A, Raza MQ, Patel K, Min D, et al. Degenerative mitral stenosis: unmet need for percutaneous interventions. Circulation. 2016;133(16):1594-604.

10. Lindman BR, Clavel M-A, Mathieu P, Iung B, Lancellotti P, Otto CM, et al. Calcific aortic stenosis. Nature reviews Disease primers. 2016;2(1):1-28.

11. Gomel MA, Lee R, Grande-Allen KJ. Comparing the role of mechanical forces in vascular and valvular calcification progression. Frontiers in cardiovascular medicine. 2019;5:197.

12. Chan JJ, Cupples LA, Kiel DP, O'Donnell CJ, Hoffmann U, Samelson EJ. QCT volumetric bone mineral density and vascular and valvular calcification: the Framingham Study. Journal of Bone and Mineral Research. 2015;30(10):1767-74.

13. Rajamannan NM, Subramaniam M, Rickard D, Stock SR, Donovan J, Springett M, et al. Human aortic valve calcification is associated with an osteoblast phenotype. Circulation. 2003;107(17):2181-4.

14. Hyder JA, Allison MA, Wong N, Papa A, Lang TF, Sirlin C, et al. Association of coronary artery and aortic calcium with lumbar bone density: the MESA Abdominal Aortic Calcium Study. American journal of epidemiology. 2009;169(2):186-94.

15. Sugihara N, Matsuzaki M. The influence of severe bone loss on mitral annular calcification in postmenopausal osteoporosis of elderly Japanese women. Japanese circulation journal. 1993;57(1):14-26.

16. Davutoglu V, Yilmaz M, Soydinc S, Celen Z, Turkmen S, Sezen Y, et al. Mitral annular calcification is associated with osteoporosis in women. American Heart Journal. 2004;147(6):1113-6.

17. Aksoy Y, Yagmur C, Tekin GO, Yagmur J, Topal E, Kekilli E, et al. Aortic valve calcification: association with bone mineral density and cardiovascular risk factors. Coronary artery disease. 2005;16(6):379-83.

18. Choi HS, Rhee Y, Hur NW, Chung N, Lee EJ, Lim SK. Association between low bone mass and aortic valve sclerosis in Koreans. Clinical endocrinology. 2009;71(6):792-7.

19. Tankó LB, Christiansen C, Cox DA, Geiger MJ, McNabb MA, Cummings SR. Relationship between osteoporosis and cardiovascular disease in postmenopausal women. Journal of Bone and Mineral Research. 2005;20(11):1912-20.

20. Schulz E, Arfai K, Liu X, Sayre J, Gilsanz V. Aortic calcification

and the risk of osteoporosis and fractures. The Journal of Clinical Endocrinology & Metabolism. 2004;89(9):4246-53.

21. Naves M, Rodríguez-García M, Díaz-López JB, Gómez-Alonso C, Cannata-Andía JB. Progression of vascular calcifications is associated with greater bone loss and increased bone fractures. Osteoporosis International. 2008;19:1161-6.

22. Organization WH. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: report of a WHO study group [meeting held in Rome from 22 to 25 June 1992]: World Health Organization; 1994.

23. Armstrong WF, Ryan T. Feigenbaum's echocardiography: Lippincott Williams & Wilkins; 2012.

24. Abramowitz Y, Jilaihawi H, Chakravarty T, Mack MJ, Makkar RR. Mitral annulus calcification. Journal of the American College of Cardiology. 2015;66(17):1934-41.

25. Coffey S, Cox B, Williams MJ. The prevalence, incidence, progression, and risks of aortic valve sclerosis: a systematic review and meta-analysis. Journal of the American College of Cardiology. 2014;63(25 Part A):2852-61.

26. Nam H-S, Shin M-H, Kweon S-S, Park K-S, Sohn S-J, Rhee J-A, et al. Association of estrogen receptor-α gene polymorphisms with bone mineral density in postmenopausal Korean women. Journal of bone and mineral metabolism. 2005;23:84-9.

27. Uçar M, Demir H. The Relationship of Brain Natriuretic Peptide Level with Biochemical Markers, Bone Mineral Density and Progenitor Factors in Rats with Experimental Osteoporosis. Journal of Anatolian Medical Research. 2022;7(1):5-12.

28. Carrai P, Camarri S, Pondrelli CR, Gonnelli S, Caffarelli C. Calcification of cardiac valves in metabolic bone disease: an updated review of clinical studies. Clinical Interventions in Aging. 2020:1085-95.

29. Arici A, Sozen I. Expression, menstrual cycle-dependent activation, and bimodal mitogenic effect of transforming growth factor-β1 in human myometrium and leiomyoma. American journal of obstetrics and gynecology. 2003;188(1):76-83.

30. Di Minno A, Zanobini M, Myasoedova VA, Valerio V, Songia P, Saccocci M, et al. Could circulating fetuin A be a biomarker of aortic valve stenosis? International journal of cardiology. 2017;249:426-30.

31. Carracedo M, Bäck M. Fetuin A in aortic stenosis and valve calcification: not crystal clear. International journal of cardiology. 2018;265:77-8.

32. Aylin S, Uslu T. The relationship between fetuin-A and bone mineral density in postmenopausal osteoporosis. Archives of Rheumatology. 2013;28(3):195-201.

33. Massera D, Trivieri MG, Andrews JP, Sartori S, Abgral R, Chapman AR, et al. Disease activity in mitral annular calcification: a multimodality study. Circulation: Cardiovascular Imaging. 2019;12(2):e008513.

34. von Mühlen DG, Greendale GA, Garland CF, Wan L, Barrett-Connor E. Vitamin D, parathyroid hormone levels and bone mineral density in community-dwelling older women: the Rancho Bernardo Study. Osteoporosis International. 2005;16:1721-6.

35. Lee T-L, Lee M-H, Chen Y-C, Lee Y-C, Lai T-C, Lin HY-H, et al. Vitamin D attenuates ischemia/reperfusion-induced cardiac injury by reducing mitochondrial fission and mitophagy. Frontiers in Pharmacology. 2020;11:604700.

36. Verdoia M, Pergolini P, Rolla R, Nardin M, Schaffer A, Barbieri L, et al. Impact of high-dose statins on vitamin D levels and platelet function in patients with coronary artery disease. Thrombosis Research. 2017;150:90-5.

37. Christodoulidis G, Vittorio TJ, Fudim M, Lerakis S, Kosmas CE. Inflammation in coronary artery disease. Cardiology in review. 2014;22(6):279-88.

38. Chitalia N, Ismail T, Tooth L, Boa F, Hampson G, Goldsmith D, et al. Impact of vitamin D supplementation on arterial vasomotion, stiffness and endothelial biomarkers in chronic kidney disease patients. PloS one. 2014;9(3):e91363.