Research Article

Is there a cross talk between aortic valve calcification and bone mineral density in older adult men and women? A single-center study from Iran

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Abstract

Despite numerous studies, the association between osteoporosis and aortic valve calcification is not clear. This study aimed to investigate the relationship between aortic valve calcification and osteoporosis in an Iranian population over 60. In this cross-sectional study, patients aged over 60 years referring to the Bone Mineral Densitometry center of Baqiyatallah Hospital (Tehran, Iran) during 2019-2020 were evaluated. Trans-thoracic echocardiography was done for all patients to evaluate the existence of aortic valve calcification. Patients were compared in two groups with and without osteoporosis (T-score < -2.5) as well as in two groups with and without aortic calcification. Two-hundred patients with a mean age of 65.92 ± 5.59 years and a mean body mass index (BMI) of 25.73 ± 4.08 kg/m2 were studied (84.5% female). Patients with osteoporosis (n=104) had lower BMI and greater frequency of aortic calcification compared to the patients without osteoporosis (n = 96). Patients with aortic calcification had higher age, lower BMI, and higher proportion of osteoporosis compared to the patients without aortic calcification (P<0.05). According to the results, it is suggested that elderly patients with osteoporosis and hypertension be evaluated for aortic valve calcification. This evaluation seems more crucial for older people with high blood pressure, lower BMI, and osteoporosis. Moreover, patients with aortic valve calcification could be evaluated for osteoporosis. Confirming the above results requires further investigation with a larger sample size.

Key Words: **Aortic calcification, Aortic stenosis, Bone density, Elderly, Osteoporosis**

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Introduction

Aortic valve sclerosis without any stenosis is prevalent in the elderly. This problem is usually diagnosed accidentally by a murmur on physical examination, echocardiography, or CT scan performed for other reasons. This sclerosis can lead to valve stenosis or can be a sign of increased cardiovascular risk factors (Freeman & Otto, 2005). Studies with a population younger than 60 years old showed a prevalence of less than 10% (Coffey et al., 2014). Among the European adults, this prevalence was 7% in the 35-44 age group, while it was 65% in the 75-84 age group (Stritzke et al., 2009). According to previous studies, aortic valve sclerosis occurs in about a quarter of people over 65 (Freeman & Otto, 2005; Otto et al., 1999). There are some similarities between the pathogenesis of both aortic valve sclerosis and atherosclerosis, including high cholesterol level, obesity, inflammation, smoking, hypertension, and calcification. Valve calcification exists in more advanced stages of this disorder (Bossé et al., 2008; O'Brien, 2006; Pasipoularides, 2016).

The world prevalence of aortic valve calcification is 12.6 million, with an increasing pattern between 1990 and 2017. This prevalence was the same among men and women. The highest prevalence is among the age group over 70 years, and the mortality due to this disorder is equal to 102700 deaths in one year alone (2017). Iran is estimated to be among the regions with a lower-than-average prevalence (Yadgir et al., 2020). Aortic calcification and atherosclerotic heart disease have some shared risk factors. However, antihypertensive medications and statins could not prevent the progression of aortic calcification (Chan et al., 2010). Impaired level of mineral metabolisms seems to be associated with aortic valve sclerosis. In the Cardiovascular Health Study, 0.5 mg/dL decrease in serum phosphate concentration increased the probability of aortic valve calcification by 17% (Linefsky et al., 2011). However, studies have shown no relationship between aortic valve sclerosis and serum levels of calcium, parathyroid hormone, and vitamin D (Adeney et al., 2009).

Moreover, bone density decreases with atherosclerosis progression, and cardiovascular disease is more common in people with osteoporosis (Bucay et al., 1998; Jie et al., 1996; Laroche et al., 2003; Laroche et al., 1994; Stojanovic et al., 2011). These two diseases have several common risk factors (Mussolino & Armenian, 2007; Ness & Aronow, 2006; Tekin et al., 2008; Varma et al., 2008; Yesil et al., 2012). Masoumi et al. found no association between coronary artery disease and osteoporosis (Tohodi et al., 2015). Also, it was shown that the incidence of coronary atherosclerosis was higher in women with osteopenia and osteoporosis than in women with a good bone density (Ness & Aronow, 2006; Varma et al., 2008). Yesil's study evaluated the men and women over 65 years and found that coronary artery disease is more common in people with osteopenia and osteoporosis than in people with enough bone density (Yesil et al., 2012). Moreover, Tekin's study showed that age is the only important factor in reducing bone density in postmenopausal women (Tekin et al., 2008).

Despite numerous studies, the association between osteoporosis and aortic valve calcification is not clear. Hence, this study aimed to investigate the relationship between aortic valve calcification and osteoporosis in patients over 60 years who referred to the bone mineral densitometry center.

Materials and Methods

Study population

Patients aged over 60 years who referred to the Bone Mineral Densitometry center of Baqiyatallah Hospital (Tehran, Iran) during 2019-2020 were considered as the sampling frame. All BMDs were indicated and ordered by a specialist physician. Patients were included if they were not the known cases of osteoporosis and had consent to participate. Patients were excluded if they did not return for the follow-ups. The patients with chronic renal failure, liver diseases, cardiovascular diseases, and rheumatoid diseases were also excluded from the study. Likewise, the patients were excluded in case of chronic corticosteroid consumption and the history of taking anti-osteoporosis medications.

Evaluating the Subjects

The patients' BMD was assessed by dual-energy X-Ray absorptiometry (DXA) in a unique center using the same equipment (Hologic QDR 4500W bone densitometer, Marlborough, MA, USA). DXA was evaluated in the two lumbar spine and proximal femur areas using standard techniques. The cut-off point of -2.5 for T-score was considered as osteoporosis (T-score<-2.5). The I-score score between −1 and −2.5 was considered as osteopenia (Lewiecki et al., 2008).

The patients' demographic data (age, gender, height, weight, and body mass index), history of their medications, and the existence of known underlying diseases (diabetes mellitus, hypertension, hypothyroidism, and dyslipidemia) were assessed. Patients were asked about the history of taking calcium supplements and the regular exercise program.

A fasting sample of five-milliliter blood was obtained from all the patients. The serum levels of fasting blood glucose, low-density lipoprotein (LDL), calcium, phosphorus, creatinine, 25-(OH) D, and parathyroid hormone (PTH) were measured. The vitamin D kit (Abbott Diagnostics, IL, USA) by a chemiluminescence microparticle immunoassay method and PTH kit (Roche, Germany) electrochemiluminescence immunoassay (ECLIA) method were used. The serum calcium (mg/dL) was measured using Cresolphthalein complexone, and total serum calcium was corrected for serum albumin.

A trans-thoracic echocardiography was done for all the patients to evaluate the existence of aortic valve calcification. All echocardiograms were done by an expert cardiologist using the same equipment (Vivid 7 ultrasound machine, GE Medical Systems, Milwaukee, Wis, and M4S probe). The existence of calcified aortic valve was assessed by the Simpson's rule method in the left lateral decubitus position based on the American Society of Echocardiography guideline (Lang et al., 2015).

Statistical analysis

The patients' data were analyzed using the statistical package for social sciences (SPSS v.21, IBM Co., Armonk, NY, USA). The patients were divided into two the subgroups of with and without osteoporosis and also with and without the aortic valve calcification. The quantitative variables were compared between the two groups using the independent samples t-test if they had a normal distribution (approved by one-sample K-S test). The qualitative variables were compared between the two groups using the Chi2 and Fisher exact tests. The relative-risk (RR) for comparing the two groups of patients with and without osteoporosis, and odds-ratio (OR) for comparing the two groups of patients with and without aortic valve calcification were measured. The binary logistic regression analysis with forward WALD method was used to remove the possible confounding effect of other variables on the relationship between osteoporosis and aortic valve calcification. The receiver operating characteristic (ROC) curve was used to evaluate the accuracy of the T-score to differentiate the patients with and without aortic valve calcification. A P-value of less than 0.05 was considered as statistically significant.

Results

Description of patients' characteristics

Table 1. Comparing the patients with and without osteoporosis (spinal or femoral area) regarding their demographic data, underlying diseases, risk factors, laboratory data, and the existence of aortic valve calcification.

Variables	Osteoporotic (N = 104)	Non-Osteoporotic (N = 96)	P value
Age, y	66.56 ± 5.76	65.23 ± 5.36	0.094
Gender, male/female	14/90	17/79	0.263
Body mass index, kg/m^2	27.66 ± 3.95	29.89 ± 3.92	< 0.001
Diabetes mellitus	16 (15.4)	19 (19.8)	0.263
Hypertension	28 (26.9)	35 (36.5)	0.147
Systolic blood pressure, mmHg	12.24 ± 1.82	12.53 ± 1.89	0.269
Hypothyroidism	11 (10.6)	18 (18.8)	0.101
Dyslipidemia	38 (36.6)	43 (44.8)	0.141
Calcium supplement			0.060
Current using	38 (36.5)	52 (54.2)	
Previous using	5 (4.8)	5 (5.2)	
Duration of using, years	4.26 ± 4.11	5.03 ± 4.40	0.420
Regular exercise program	49 (47.1)	51 (53.1)	0.396
Aortic valve calcification	33 (31.7)	19 (19.8)	0.039
Serum 25-OH-D_3, mg/dL	38.55 ± 19.53	36.74 ± 16.15	0.479
Serum parathyroid hormone, mg/dL	45.88 ± 30.69	49.77 ± 29.82	0.371
Serum calcium, mg/dL	9.51 ± 1.17	9.51 ± 1.01	0.960
Serum phosphorus, mg/dL	3.89 ± 0.64	3.94 ± 0.79	0.653
Fasting blood glucose, mg/dL	106.02 ± 24.61	109.02 ± 19.32	0.343
Low density lipoprotein, mg/dL	120.58 ± 37.7	110.89 ± 36.4	0.067
Serum creatinine, mg/dL	1.10 ± 0.84	1.08 ± 0.48	0.853

Two-hundred people who referred to the BMD center were evaluated. The overall mean age of the participants was 65.92 ± 5.59 years and their mean BMI was 25.73 ± 4.08 kg/m2. Patients were 15.5% male and 84.5% female, 17.5% of them were known cases of diabetes mellitus, 31.5% hypertension, 14.5% hypothiro-idism, and 39.5% dyslipidemia. Three patients were smokers, and no patient was a current alcohol consumer.

According to the bone densitometry, the mean T-score was -1.61 ± 1.63 and -1.44 ± 1.12 in the spine and femur areas. The overall prevalence of osteoporosis (T-Score < -2.5) was 52.0% (45.5% in the spine area, 22.5% in the femur area, and 16.0% in both areas). Echocardiographic evaluations showed that 52 patients (26.0%) had aortic valve calcification.

Comparing the patients with and without osteoporosis

There were no significant differences between the patients with and without osteoporosis regarding their age and gender. Although there was no significant correlation between the patients' spinal T-score and their age (P=0.234), the patients' femoral T-score was significantly correlated with their age (P=0.031, R=-0.153). The mean BMI was significantly lower in osteoporotic patients compared to the non-osteoporotic subjects (27.66 vs. 29.89 kg/m2, P<0.001).

Patients with and without osteoporosis had no significant differences regarding their underlying diseases, systolic blood pressure, calcium supplementation, and regular exercise program (P>0.05, Table 1). Osteoporotic patients were more likely to have the calcified aortic valve than the non-osteoporotic subjects (31.7% vs. 19.8%, P=0.039, RR=1.603). There were no significant differences between the patients with and without osteoporosis regarding their laboratory data (P>0.05, Table 1).

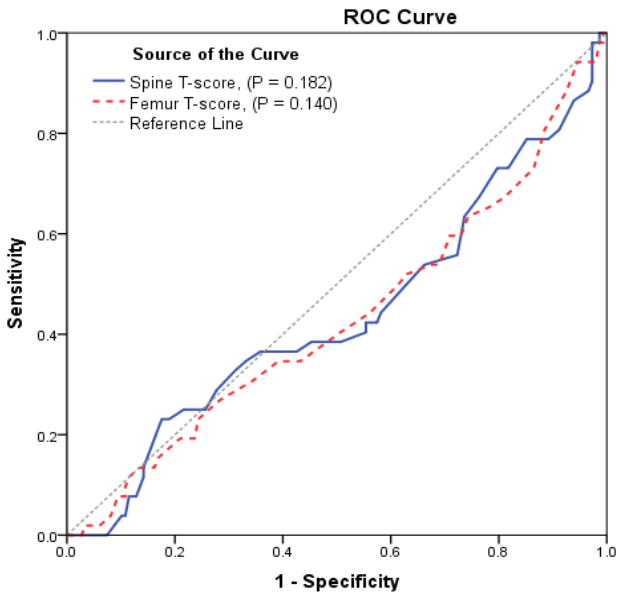

Figure 1. The receiver operating characteristic (ROC) curve evaluating the accuracy of the bone mineral densitometry (T-score) in both spinal and femoral areas to differentiate the patients with and without aortic valve calcification.

Seventeen variables were entered into the regression model comparing the patients with and without osteoporosis. After three steps, four variables of aortic valve calcification (P=0.044), the patients' BMI (P=0.001), serum LDL (P=0.045), and current calcium supplementation (P=0.030) remained in the regression model for prediction of osteoporosis (P=0.003, R2=0.253).

Comparing the Patients with and without Aortic Valve Calcification

There were no significant differences between the patients with and without aortic valve calcification regarding their age and gender. The mean BMI was significantly lower in patients with aortic valve calcification compared to the others (27.81 vs. 29.06 kg/m2, P=0.042). The proportion of known hypertensive patients was significantly higher in patients with calcified aortic valve compared to the subjects without aortic valve calcification (46.2% vs. 25.6% P=0.008). Also, the mean systolic blood pressure was significantly higher in patients with calcified aortic valve compared to the subjects without aortic valve calcification (P=0.035). There were no significant differences between the patients with and without calcified aortic valve regarding their other underlying diseases, calcium supplementation, and regular exercise program (P>0.05, Table 2). There were also no significant differences between the patients with and without osteoporosis regarding their laboratory data (P>0.05, Table 2).

Furthermore, the mean T-score in both femoral and spinal areas were not significantly different between the patients with and without the calcified aortic valve (P>0.05, Table 3). The proportion of patients with osteoporosis of the spinal area was not significantly different between the patients with and without aortic valve calcification (55.8% vs. 41.9%, P=0.059, OR=1.749). The proportion of patients with femoral osteoporosis was significantly higher in patients with the calcified aortic valve than in the people without aortic calcification (32.7% vs. 18.9%, P=0.034, OR=2.082). One-hundred and four patients had osteoporosis in at least one area (femur or spine area). The proportion of patients having osteoporosis in at least one area was significantly higher among the patients with the calcified aortic valve compared to the people without aortic calcification (63.5% vs. 48.0%, P=0.039, OR=1.884). Also, 32 patients had both femoral and spinal osteoporosis. The proportion of patients with osteoporosis in both areas was significantly higher in patients with the calcified aortic valve than the people without aortic calcification (25.0% vs. 12.8%, P=0.036, OR=2.263, Table 3).

Seventeen variables were entered into the regression model comparing the patients with and without aortic valve calcification. After two steps, four variables of osteoporosis (P=0.031), the patients' BMI (P=0.021), serum PTH (P=0.048), and hypertension (P=0.001) remained in the regression model for prediction of aortic valve calcification (P=0.037, R2=0.123).

The Relationship between Aortic Valve Calcification and T-score using the ROC Curve

The ROC curve was created to evaluate the ability of the T-score to predict the existence of aortic valve calcification. The area under the curve was 0.438 for spinal T-score and 0.431 for femoral T-score. None of the T-scores could predict the existence of aortic valve calcification (P>0.05, figure 1).

Table 2. Comparing the patients with and without aortic valve calcification regarding their demographic data, underlying diseases, risk factors, and laboratory data.

Variables	Aortic valve calcification		P value
	Yes (N = 52)	No (N = 148)	
Age, y	67.19 ± 5.33	65.47 ± 5.61	0.050
Gender, male/female	10/42	21/127	0.388
Body mass index, kg/m^2	27.81 ± 3.56	29.06 ± 4.21	0.042
Diabetes mellitus	12 (23.1)	23 (15.5)	0.154
Hypertension	24 (46.2)	39 (26.4)	0.008
Systolic blood pressure, mmHg	12.22 ± 1.57	12.85 ± 2.46	0.035
Hypothyroidism	7 (13.5)	22 (14.9)	0.805
Dyslipidemia	22 (42.3)	57 (38.5)	0.630
Calcium supplement			0.200
Current using	18 (34.6)	71 (48.0)	
Previous using	2 (3.8)	8 (5.4)	
Duration of using, years	4.31 ± 4.30	4.62 ± 4.21	0.794
Continues exercise	29 (55.8)	71 (48)	0.333
Serum 25-OH-D_3, mg/dL	37.43 ± 17.11	37.76 ± 18.32	0.908
Serum parathyroid hormone, mg/dL	42.31 ± 25.30	49.71 ± 31.70	0.134
Serum calcium, mg/dL	9.59 ± 0.44	9.48 ± 1.24	0.555
Serum phosphorus, mg/dL	3.93 ± 0.65	3.91 ± 0.74	0.886
Fasting blood glucose, mg/dL	105.91 ± 18.50	108.03 ± 23.40	0.574
Low density lipoprotein, mg/dL	110.34 ± 40.21	117.91 ± 36.13	0.205
Serum creatinine, mg/dL	1.02 ± 0.13	1.11 ± 0.79	0.191

Discussion

This study evaluated the relationship between the BMD and aortic valve calcification in a population of over 60 years. The aortic valve calcification was 11.9% higher in osteoporotic patients than that in the non-osteoporotic ones. In addition, osteoporosis was more prevalent in patients with aortic valve calcification than the others.

Massera et al. showed no association between the patients' BMD and calcification (aortic valvular, aortic annular and mitral annular calcifications). In addition, they found no significant difference between the patients with and without osteoporosis in terms of calcification. Similar to our results, Massera et al. showed a relationship between hip osteoporosis and aortic valve calcification in male patients. Massera et al. study had an older age (mean age of 76.8 vs. 65.92 years) and a higher proportion of males (42% vs. 15.5%) compared to the population in our study (Massera et al., 2017).

Moreover, Rodríguez et al. showed a significant inverse relationship between hip BMD and the presence of abdominal aortic calcification. This association was also observed separately in female patients, but no significant association was between BMD and aortic calcification in male patients. Patients in the Rodríguez et al. study had older age (70.5 years), higher BMI (28.1 kg/m2), and a higher proportion of males (39% males) than in our study (Rodríguez et al., 2017). Hulbert et al. examined the association between abdominal aortic calcification and BMD of three areas (femoral neck, spine, and hip). After five years of follow-up, the aortic calcification score increased, and the BMD decreased significantly. The decrease in T-score and increase in aortic calcification score were not significantly correlated to each other. Additionally, calcium supplementation (for at least five years) increased aortic calcification score. Hulbert et al. Found that calcium supplementation in female and older patients had no significant effect on BMD and abdominal aortic calcification. Patients in the Hulbert study were similar to ours in terms of gender distribution (73% female) and age (mean 65.9 years), but their patients' BMI was higher than that in the present study (28 kg/m2) (Hulbert et al., 2019). Similarly, Lewis et al. examined elderly females (mean age of 75 years) and found that patients with moderate to severe aortic calcification were more likely to have vertebral fractures in the lumbar area. They also showed that hip bone density decreases with increasing severity of abdominal aortic calcification (Lewis et al., 2019). In addition, Aleksova et al. found an indirect correlation between the trabecular bone score (TBS) and the abdominal aortic calcification score in chronic renal failure (Aleksova et al., 2018).

Several studies have examined the calcification of coronary arteries and calcified plaques of the heart with CT angiography. Ahmadi et al. showed that coronary artery calcification (Agatston score) was inversely related to BMD. This association between coronary artery calcification and BMD was significantly higher in

Table 3. Comparing the patients with and without aortic valve calcification regarding the bone densitometry results.

Variables	Aortic valve calcification		P value
	Yes (N = 52)	No (N = 148)	
T-score			
Spine area	- 1.93 ± 1.49	- 1.49 ± 1.66	0.084
Femur area	- 1.66 ± 1.05	- 1.39 ± 1.14	0.908
Osteoporosis			
Spine area	29 (55.8)	62 (41.9)	0.059
Femur area	17 (32.7)	28 (18.9)	0.034
At-least one area	33 (63.5)	71 (48.0)	0.039
Both areas	13 (25.0)	19 (12.8)	0.036

menopausal women than in others. The subjects in this study were 69% male with a mean age of 57 years (Ahmadi et al., 2018). Similarly, Zhu et al. found that patients with calcified plaque (in carotid and coronary arteries) were older, had lower BMD, and were more likely to have hypertension, diabetes, and dyslipidemia. Also, severe osteoporosis was significantly associated with calcified plaques (carotid and coronary arteries) (Zhu et al., 2019). Beckman et al. showed that as coronary artery calcification increased, cortical bone BMD increased, and central bone BMD decreased (Beckman et al., 2018). Liu et al. showed a significant relationship between BMD and the incidence of calcified plaque in the carotid artery (Liu et al., 2019).

Correspondingly, several studies examined the association of bone metabolism markers and vascular calcification. Liu et al. showed that the occurrence of the cardiovascular plaque was associated with serum levels of bone metabolism markers such as osteoprotegerin and osteocalcin (Liu et al., 2019). Patients with calcified plaque (in the carotid and coronary arteries) had higher osteoprotegerin blood levels and lower blood levels of leptin and vitamin D than patients without plaques (Zhu et al., 2019). Similar cellular mechanisms for osteoporosis and vascular calcification are suggested (García-Gómez & Vilahur, 2020; Rochette et al., 2019). Osteoporosis medications may help to treat or prevent the progression of calcification. Also, Alishiri et al. found that alendronate prescription for 21 weeks in osteoporotic patients with aortic calcification improves aortic valve gradient and cardiac enzyme NT-pro-BNP compared to the control group (Alishiri et al., 2020).

Conclusion

According to the results, a significant relationship between aortic valve calcification and osteoporosis was observed in older adults. Hence, it is suggested that elderly patients with osteoporosis and hypertension be evaluated for aortic valve calcification to prevent its progression and following aortic valve dysfunction. This evalu-

-ation seems more crucial for older people with high blood pressure, lower BMI, and osteoporosis. In addition, patients with aortic valve calcification could be evaluated for osteoporosis (as a possible cause or associated disorder) to treat and prevent its progression. Confirming the above results requires further investigation and further studies with larger sample size.

What is already known on this subject?

There are some similarities between the pathogenesis of both aortic valve sclerosis and atherosclerosis, including high cholesterol level, obesity, inflammation, smoking, hypertension, and calcification.

What this study adds?

A significant relationship and cross talk between aortic valve calcification and osteoporosis was observed in older adults.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol was approved by the National Committee for Ethics in Biomedical Research and the Ethics Committee of Baqiyatallah University of Medical Sciences (approval code: IR.BMSU.BAQ.REC.1398.013). The study protocol was explained to the patients. Entering into the study was voluntarily, and a written informed consent was obtained from all patients. The patients' data were kept secure. Also, all para-clinical evaluations were free-of-charge for the participants.

Informed consent Performed.

Author contributions

Conceptualization: S.Sh., F.S.; Methodology: A.Sh., M.M.; Software: S.Sh., A.Sh.; Validation: M.M., F.S.; Formal analysis: S.Sh.; Investigation: A.Sh., M.S.Q.; Resources: F.S.; Data curation: A.Sh.; Writing - original draft: MM., F.S.; Writing - review & editing: A.Sh.; Visualization: S.Sh.; Supervision: F.S.; Project administration: M.M.; Funding acquisition: S.Sh.

References

Adeney, K. L., Siscovick, D. S., Ix, J. H., Seliger, S. L., Shlipak, M. G., Jenny, N. S., & Kestenbaum, B. R. (2009). Association of serum phosphate with vascular and valvular calcification in moderate CKD. Journal of the American Society of Nephrology, 20(2), 381-387. doi: https://doi.org/10.1681/ASN.2008040349

Ahmadi, N., Mao, S. S., Hajsadeghi, F., Arnold, B., Kiramijyan, S., Gao, Y., . . . Budoff, M. (2018). The relation of low levels of bone mineral density with coronary artery calcium and mortality. Osteoporosis international: A Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 29(7), 1609-1616. doi: https://doi.org/10.1007/s00198-018-4524-7

Aleksova, J., Kurniawan, S., Vucak-Dzumhur, M., Kerr, P., Ebeling, P. R., Milat, F., & Elder, G. J. (2018). Aortic vascular calcification is inversely associated with the trabecular bone score in patients receiving dialysis. Bone, 113, 118-123. doi: https://doi.org/10.1016/j.bone.2018.05.014

Alishiri, G., Heshmat-Ghahdarijani, K., Hashemi, M., Zavar, R., & Farahani, M. M. (2020). Alendronate slows down aortic stenosis progression in osteoporotic patients: An observational prospective study. Journal of Research in Medical Sciences, 25(1), 65. doi: https://doi.org/10.4103/jrms.JRMS_408_20

Beckman, J. P., Camp, J. J., Lahr, B. D., Bailey, K. R., Kearns, A. E., Garovic, V. D., . . . Holmes, D. R., 3rd. (2018). Pregnancy history, coronary artery calcification and bone mineral density in menopausal women. Climacteric: The journal of the International Menopause Society, 21(1), 53-59. doi: https://doi.org/10.1080/13697137.2017.1406910

Bossé, Y., Mathieu, P., & Pibarot, P. (2008). Genomics: The next step to elucidate the etiology of calcific aortic valve stenosis. Journal of the American College of Cardiology, 51(14), 1327-1336. doi: https://doi.org/10.1016/j.jacc.2007.12.031

Bucay, N., Sarosi, I., Dunstan, C. R., Morony, S., Tarpley, J., Capparelli, C., . . . Lacey, D. L. (1998). Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. Genes & Development, 12(9), 1260-1268. URL: http://genesdev.cshlp.org/content/12/9/1260.short

Chan, K., Teo, K., Dumesnil, J., Ni, A., & Tam, J. (2010). Effect of Lipid lowering with rosuvastatin on progression of aortic stenosis: Results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. Circulation, 121(2), 306-314. doi: https://doi.org/10.1161/CIRCULATIONAHA.109.900027

Coffey, S., Cox, B., & Williams, M. J. (2014). The prevalence, incidence, progression, and risks of aortic valve sclerosis: a systematic review and meta-analysis. Journal of the American College of Cardiology, 63(25 Part A), 2852-2861. doi: https://doi.org/10.1016/j.jacc.2014.04.018

Freeman, R. V., & Otto, C. M. (2005). Spectrum of calcific aortic valve disease: Pathogenesis, disease progression, and treatment strategies. Circulation, 111(24), 3316-3326. doi: https://doi.org/10.1161/CIRCULATIONAHA.104.486738

García-Gómez, M. C., & Vilahur, G. (2020). Osteoporosis and vascular calcification: A shared scenario [Osteoporosis y calcificación vascular:

un escenario compartido]. Clinica e investigacion en arteriosclerosis: Publicacion oficial de la Sociedad Espanola de Arteriosclerosis, 32(1), 33-42. doi: https://doi.org/10.1016/j.arteri.2019.03.008

Hulbert, M., Turner, M. E., Hopman, W. M., Anastassiades, T., Adams, M. A., & Holden, R. M. (2019). Changes in vascular calcification and bone mineral density in calcium supplement users from the Canadian Multi-center Osteoporosis Study (CaMOS). Atherosclerosis, S0021-9150(0019)31609-31600. doi: https://doi.org/10.1016/j.atherosclerosis.2019.12.003

Jie, K.-S., Bots, M., Vermeer, C., Witteman, J., & Grobbee, D. (1996). Vitamin K status and bone mass in women with and without aortic atherosclerosis: a population-based study. Calcified Tissue International, 59(5), 352-356. doi: https://doi.org/10.1007/s002239900139

Lang, R. M., Badano, L. P., Mor-Avi, V., Afilalo, J., Armstrong, A., Ernande, L., . . . Kuznetsova, T. (2015). Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. European Heart Journal-Cardiovascular Imaging, 16(3), 233-271. doi: https://doi.org/10.1016/j.bone.2008.08.106

Laroche, M., Moulinier, L., Leger, P., Lefebvre, D., MaziČres, B., & Boccalon, H. (2003). Bone mineral decrease in the leg with unilateral chronic occlusive arterial. Clinical and Experimental Rheumatology, 21, 103-106. doi: file:///C:/Users/1019/Downloads/article.pdf

Laroche, M., Pouilles, J., Ribot, C., Bendayan, P., Bernard, J., Boccalon, H., & Mazieres, B. (1994). Comparison of the bone mineral content of the lower limbs in men with ischaemic atherosclerotic disease. Clinical Rheumatology, 13(4), 611-614. doi: https://doi.org/10.1007/BF02243003

Lewiecki, E. M., Gordon, C. M., Baim, S., Leonard, M. B., Bishop, N. J., Bianchi, M. L., . . . Rauch, F. (2008). International Society for Clinical Densitometry 2007 adult and pediatric official positions. Bone, 43(6), 1115-1121. doi: https://doi.org/10.1016/j.bone.2008.08.106

Lewis, J. R., Eggermont, C. J., Schousboe, J. T., Lim, W. H., Wong, G., Khoo, B., . . . Prince, R. L. (2019). Association Between Abdominal Aortic Calcification, Bone Mineral Density, and Fracture in Older Women. Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research, 34(11), 2052-2060. doi: https://doi.org/10.1002/jbmr.3830

Linefsky, J. P., O'Brien, K. D., Katz, R., de Boer, I. H., Barasch, E., Jenny, N. S., . . . Kestenbaum, B. (2011). Association of serum phosphate levels with aortic valve sclerosis and annular calcification: the cardiovascular health study. Journal of the American College of Cardiology, 58(3), 291-297. doi: https://doi.org/10.1016/j.jacc.2010.11.073

Liu, D., Chen, L., Dong, S., Peng, Z., Yang, H., Chen, Y., . . . Zhou, R. (2019). Bone mass density and bone metabolism marker are associated with progression of carotid and cardiac calcified plaque in Chinese elderly population. Osteoporosis International: A Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 30(9), 1807-1815. doi: https://doi.org/10.1007/s00198-019-05031-5

Massera, D., Xu, S., Bartz, T. M., Bortnick, A. E., Ix, J. H., Chonchol, M., . . . Kizer, J. R. (2017). Relationship of bone mineral density with valvular and annular calcification in community-dwelling older people: The cardiovascular health study. Archives of Osteoporosis, 12(1), 52-52. doi: https://doi.org/10.1007/s11657-017-0347-y

Mussolino, M. E., & Armenian, H. K. (2007). Low bone mineral density, coronary heart disease, and stroke mortality in men and women. The Third National Health and Nutrition Examination Survey, Annals of Epidemiology, 17(11), 841-846. doi: https://doi.org/10.1016/j.annepidem.2007.06.005

Ness, J., & Aronow, W. S. (2006). Comparison of prevalence of atherosclerotic vascular disease in postmenopausal women with osteoporosis or osteopenia versus without osteoporosis or osteopenia. The American Journal of Cardiology, 97(10), 1427-1428. doi: https://doi.org/10.1016/j.amjcard.2005.12.033

O'Brien, K. D. (2006). Pathogenesis of calcific aortic valve disease: a disease process comes of age (and a good deal more). Arteriosclerosis, Thrombosis, and Vascular Biology, 26(8), 1721-1728. doi: https://doi.org/10.1016/j.amjcard.2005.12.033

Otto, C. M., Lind, B. K., Kitzman, D. W., Gersh, B. J., & Siscovick, D. S. (1999). Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. New England Journal of Medicine, 341(3), 142-147. doi: https://doi.org/10.1056/NEJM199907153410302

Pasipoularides, A. (2016). Calcific aortic valve disease: part 1—molecular pathogenetic aspects, hemodynamics, and adaptive feedbacks. Journal of Cardiovascular Translational Research, 9(2), 102-118. doi: https://doi.org/10.1007/s12265-016-9679-z

Rochette, L., Meloux, A., Rigal, E., Zeller, M., Malka, G., Cottin, Y., & Vergely, C. (2019). The Role of osteoprotegerin in vascular calcification and bone metabolism: The basis for developing new therapeutics. Calcified Tissue International, 105(3), 239-251. doi: https://doi.org/10.1007/s00223-019-00573-6

Rodríguez, A. J., Scott, D., Hodge, A., English, D. R., Giles, G. G., & Ebeling, P. R. (2017). Associations between hip bone mineral density, aortic calcification and cardiac workload in community-dwelling older Australians. Osteoporosis International : A Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 28(7), 2239-2245. doi: https://doi.org/10.1007/s00198-017-4024-1

Stojanovic, O. I., Lazovic, M., Lazovic, M., & Vuceljic, M. (2011). Association between atherosclerosis and osteoporosis, the role of vitamin D. Archives of Medical Science: AMS, 7(2), 179. doi: https://doi.org/10.5114/aoms.2011.22066

Stritzke, J., Linsel-Nitschke, P., Markus, M. R. P., Mayer, B., Lieb, W.,

Luchner, A., . . . Hense, H.W. (2009). Association between degenerative aortic valve disease and long-term exposure to cardiovascular risk factors: Results of the longitudinal population-based KORA/MONICA survey. European Heart Journal, 30(16), 2044-2053. doi: https://doi.org/10.1093/eurheartj/ehp287

Tekin, G. O., Kekilli, E., Yagmur, J., Uckan, A., Yagmur, C., Aksoy, Y., . . . Yetkin, E. (2008). Evaluation of cardiovascular risk factors and bone mineral density in post-menopausal women undergoing coronary angiography. International Journal of Cardiology, 131(1), 66-69. doi: https://doi.org/10.1016/j.ijcard.2007.09.002

Tohodi, M., Dabbaghmanesh, M. H., Kojuri, J., & Khedri, M. (2015). Relation between bone mineral density and coronary artery disease. ISMJ, 17(6), 1195-1202. URL: http://ismj.bpums.ac.ir/browse.php?a_id=636&sid=1&slc_lang=en

Varma, R., Aronow, W. S., Basis, Y., Singh, T., Kalapatapu, K., Weiss, M. B., . . . Monsen, C. E. (2008). Relation of bone mineral density to frequency of coronary heart disease. The American Journal of Cardiology, 101(8), 1103-1104. doi: https://doi.org/10.1016/j.amjcard.2007.12.013

Yadgir, S., Johnson, C. O., Aboyans, V., Adebayo, O. M., Adedoyin, R. A., Afarideh, M., . . . Arabloo, J. (2020). Global, regional, and national burden of calcific aortic valve and degenerative mitral valve diseases, 1990–2017. Circulation, 141(21), 1670-1680. doi: https://doi.org/10.1161/CIRCULATIONAHA.119.043391

Yesil, Y., Ulger, Z., Halil, M., Halaçlı, B., Yavuz, B. B., Yeşil, N. K., . . . Ariogul, S. (2012). Coexistence of osteoporosis (OP) and coronary artery disease (CAD) in the elderly: It is not just a by chance event. Archives of Gerontology and Geriatrics, 54(3), 473-476. doi: https://doi.org/10.1016/j.archger.2011.06.007

Zhu, J., Guo, F., Zhang, J., & Mu, C. (2019). Relationship between carotid or coronary artery calcification and osteoporosis in the elderly. Minerva Medica, 110(1), 12-17. doi: https://doi.org/10.23736/S0026-4806.18.05632-X