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# Aortic Valve Calcification: Assessment of Cardiovascular Risk Factors and Bone Mineral Density in Patients Undergoing Coronary Angiography

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Objective: Aortic valve calcification (AVC) appears to have high incidence of cardiovascular risk factors and can be considered as a manifestation of atherosclerosis. Association between low bone mineral density (BMD) and increased prevalence of aortic calcification has been shown in older women mainly in population based studies. However, some studies have reported lack of association between BMD and aortic calcification. Accordingly we aimed to assess AVC in patients undergoing coronary angiography and to compare cardiovascular risk factors and BMD of patients with and without AVC.
Materials and Methods: Study population consisted of 585 consecutive patients (372 male, 213 female mean age 59□ 10) who underwent coronary angiography. Complete transthoracic echocardiography studies were performed in all patients. AVC was defined as bright dense echos of >1 mm size on one or more cusps and decreased mobility of the involved cusp. All patients were referred to Nuclear Medicine department to measure bone mineral density (T score) using the dual energy x-ray absorptiometry method (DEXA). Age, sex, body mass index, hypertension, diabetes mellitus, coronary artery disease, hypercholesterolemia, and smoking status were recorded in all patients.
Results: The prevalence of AVC in our study population was found to be 27% (160/585). There were not statistically significant differences between two groups in respect to diabetes mellitus, hypercholesterolemia, smoking status ($p>0.05$ for all). Age and hypertension were found to be independent positive risk factors for AVC, where as body mass index was found to be negatively and independently associated with AVC. Presence of coronary artery disease was significantly higher in patients with AVC compared to those without AVC however it was not found to be associated with AVC. Neither T score nor age- and gender adjusted T score were found to be associated with AVC.
Conclusion: We have demonstrated that age, hypertension, and body mass index are independently associated with AVC. Age-gender adjusted T score measuring BMD is found to be independent of AVC. Although we have shown absence of association between coronary artery disease and AVC, this issue remains to be clarified in further clinical studies.

**Key Words:** Aortic valve calcification, Bone mineral density, Cardiovascular risk factors, Coronary artery disease, Atherosclerosis, Osteoporosis, T score

**Aort Kapak kalsifikasyonu: Koroner Anjiografi Yapılan Hastalarda Kardiyovasküler Risk Faktörlerinin ve Kemik Mineral Dansitesinin Değerlendirilmesi**

Amaç: Aort kapak kalsifikasyonu (AKK) yüksek kardiyovasküler risk insidansına sahip görünmekte olup, aterosklerozun bir sonucu olarak kabul edilebilir. Düşük kemik mineral dansitesi ve artmış aort kalsifikasyon prevalensi arasındaki ilişki esas olarak toplum tabanlı çalışmalarda yaşlı bayanlarda gösterilmiştir. Ancak bazı çalışmalar kemik mineral dansitesi ile aort kalsifikasyonu arasında ilişki olmadığını bildirmiştir. Bu yüzden. biz koroner angiografi yapılan hastalarda AKK'nu değerlendirmeyi ve AKK olan ve olmayan hastaların kardiyovasküler risk faktörlerini ve kemik mineral dansitelerini karşılaştırmayı amaçladık.
Materyal ve metod: Çalışma populasyonu koroner angiografi yapılan 585 ardışık hasta (372 erkek, 213 kadın, ortalama yaş=59±10 yıl) içeriyordu. Bütün hastalara transtorasik ekokardiyografik inceleme yapıldı. AKK bir yada daha fazla küspis üzerinde birden fazla parlak yoğun ekoların izlenmesi ve tutulan küspisin azalmış hareketi olarak tanımlandı. Bütün hastalar dual energy x-ray absorpsiyometri (DEXA) yöntemi ile kemik mineral dansitesi (T scor) ölçümü için Nükleer Tıp bölümüne yönlendirildi. Tüm hastalarda yaş, cinsiyet, vücut kitle indeksi, hipertansiyon, diyabetes mellitus, koroner arter hastalığı, hiperkolesterolemi ve sigara içiciliği kaydedildi.

Bulgular: Çalışmamızda AKK prevalensı %27 (160/585) bulundu. Her iki grup arasında diyabetes mellitus, hiperkolesterolemi ve sigara içiciliği yönünden istatistiksel olarak anlamlı fark yoktu (p>0.05 hepsi için). Yaş ve hipertansiyon AKK için bağımsız risk faktörü olmasına karşılık vücut kitle indeksi AKK için bağımsız ve negatif risk faktörü olarak saptandı. AKK ile ilişkili bulunmasada AKK olan grupta koroner arter hastalığı anlamlı oranda yüksek saptandı. Ne T skoru, ne de yaş ve cinsiyete uyarlanmış T skoru AKK ile ilişkili bulunmadı.
Sonuç: Biz bu çalışmada yaş, hipertansiyon ve vücut kitle indeksi ile AKK arasında bağımsız ilişki olduğunu gösterdik. Kemik mineral dansite ölçümünde yaş-cinsiyet uyarlanmış T skoru AKK ile ilişkisiz bulundu. Her ne kadar çalışmamızda koroner arter hastalığı ile AKK arasında ilişki olmadığı gösterilmiş olsada bu konunun aydınlanması için ileri çalışmalara ihtiyaç vardır.

**Anahtar Kelimeler:** Aort kapak kalsifikasyonu, Kemik mineral dansitesi, Kardiyovasküler risk faktörleri, Koroner arter hastalığı, Ateroskleroz, Osteoporoz, T scor

Aortic valve calcification (AVC) has a prevalence of 25% in patients above the age of 65 years[1] and has been associated with a 50% increase in risk for cardiovascular mortality.[2] The association between AVC and cardiovascular risk factors, namely hypercholesterolemia, diabetes mellitus, hypertension, cigarette smoking, male sex, and age has been shown by several reports.[1,3-8] Additionally, new observational and in vitro studies support the hypothesis that calcific valvular aortic stenosis is the result of active bone formation rather then a passive process.[9, 10] Aortic valve calcification appears to have similar etiology and high incidence of cardiovascular risk factors and can be considered as a manifestation of atherosclerosis.

Association between low bone mineral density (BMD) and increased prevalence of aortic calcification has been shown in older women mainly in population based studies.[11, 12] Osteoporosis and low BMD are often present in patients with vascular calcification[13-15] and the composition of calcified plaque is similar to bone mineral hydroxyapatite, suggesting that the two conditions may be interrelated.[16] However, the pathophysiologic mechanisms underlying this association are unknown. Recently we have shown that AVC is positively associated with age and hypertension but negatively with bone mineral density in patients recruited from the echocardiography laboratory.[3] However, some studies have reported lack of association between BMD and aortic calcification.[17, 18] Accordingly we aimed to assess AVC in patients undergoing coronary angiography and to compare cardiovascular risk factors and BMD of patients with and without AVC.

## MATERIAL AND METHODS

### Study group

Study population consisted of 585 consecutive patients (372 male, 213 female mean age 59=60±10) who underwent coronary angiography. Patients with rheumatic heart disease, hypertrophic obstructive cardiomyopathy, renal failure, taking hormone replacement treatment, and osteoporosis treatment were not included in the study. All patients enrolled in the study gave informed consent and hospital ethics committee approved the study protocol.

### Transthoracic echocardiography

Complete transthoracic echocardiography (TTE) studies were performed in all patients with a commercially available system (ATL 5000 HD, Bothell, Washington, USA) and 4 MHz Probe. AVC was defined as bright dense echos of >1 mm size on one or more cusps and decreased mobility of the involved cusp.

Two highly experienced cardiologists blinded to the measurement of BMD as assessed with DEXA and clinical data of the patients performed the echocardiographic evaluation. The patient was selected for the study only when both investigators were in agreement about the absence or presence of AVC. Eighteen patients were not included in the study because of the disagreement between the echocardiographers.

### Risk Factors

The following clinical and demographic parameters were recorded: age, sex, body mass index (BMI), hypertension (known hypertension treated with antihypertensive drugs, two or more blood pressure recordings greater than 140/90 mm Hg), diabetes mellitus (known diabetes treated with diet or drugs or both; or either a fasting serum glucose of more than 126 mg/dl), coronary artery disease (CAD) (angiographycally proven coronary lesions ≥50%, previous percutaneous coronary intervention), hypercholesterolemia (known treated hypercholesterolemia or fasting or non-fasting serum cholesterol concentrations higher than 200 mg/dl). Current cigarette smoking was defined as active smoking within the past 12 months.

**Coronary Angiography and Bone Mineral Density Measurement**

Coronary angiography procedure was performed with the standard Judkin's technique. Patients underwent coronary angiography in our clinic due to the presence of documented myocardial infarction, typical chest pain, and atypical chest pain with positive or equivocal results of noninvasive screening tests for myocardial ischemia. All patients were referred to Nuclear Medicine department to measure BMD using the dual energy x-ray absorptiometry method (DEXA). Each of the 2 tests was interpreted by observers who were unaware of the results of the other test. Transthoracic echocardiography and BMD measurement were performed on the same day, before or the day after coronary angiography. Measurements were performed in the anteroposterior (AP) view for the lumbar spine with a DEXA scanner (Hologic QDR4500 Elite, Bedford, Mass). The AP spine measurement was performed over the L1 to L4 vertebrae. The BMD value for each region was calculated as the ratio of bone mineral content to the area of the interested region (g/ cm2). For their T-score values, the patients were grouped as having osteoporosis, having osteopenia, or being normal according to the World Health Organization (WHO) diagnostic criteria for osteoporosis defined in 1994.[19] The T-score indicates the difference between the patient' BMD and the mean BMD of healthy young adults, matched for sex and ethnic group, and is expressed in SD units. When the individual T-score value was ≤-2.5 at the spine or hip, osteoporosis was diagnosed; a T-score between -2.5 and -1 was classified as osteopenia; and a T-score ≥-1 was regarded as normal or healthy.

**Statistical analysis**

Numerical variables were reported as the mean SD and categorical variables were presented as percentage. Comparison of cardiovascular risk factors and BMD in patients with and without AVC was performed respectively using the Chi-square test or unpaired t test. Logistic regression analysis was employed to detect possible significant associations between AVC, and a number of independent variables (age, hypertension, T score, BMI, and coronary artery disease). In contrast to the other variables, age, BMI and T score were modeled as a continuous variable. Variable selection was terminated when no candidate variables for entry were significant at $P<0.05$, and all those selected for entry remained significant at $P<0.10$. All tests of statistical significance were two-tailed and were considered to be significant at a 0.05 level of statistical significance. Statistical analyses were performed with SPSS statistical software (version 10.0, SPSS, Chicago, IL, USA).

## RESULTS

***Cardiovascular Risk Factors and AVC***

Baseline characteristics of patients are presented in Table-1. The prevalence of AVC in our study population was found to be 27% (160/585). There were not statistically significant differences between two groups in respect to diabetes mellitus, hypercholesterolemia, smoking status ($p>0.05$ for all, Table-I). Prevalence of hypertension, and mean age of the patients with AVC were significantly higher than those without AVC. Systolic blood pressure of AVC patients were significantly higher than that of patients without AVC (139±23 mmHg vs 133±22 mmHg $p=0.02$) however diastolic blood pressure were comparable between two groups (82±11 mmHg vs 81±11 mmHg $p=0.17$). Patients without AVC were taller (166±9 cm vs 164±10 cm $p=0.005$) and heavier (76±13 kg vs 71±12 kg $p=0.001$) and body mass index was significantly lower in patients with AVC compared to patients without AVC (Table-I). Age and hypertension were found to be independent positive risk factors for AVC, where as BMI was found to be negatively and independently associated with AVC (Table-II). Additionally there were not statistically significant difference between patients with and without AVC in respect to serum glucose levels (115±38 mg/dL vs 122±56 mg/dL $p=0.11$ respectively) creatinin levels (0.95±0.25 mg/dL vs 0.94±.42 mg/dL $p=0.8$ respectively), cholesterol levels (187±43 mg/dL vs 187±41 mg/dL $p=0.8$ respectively). Percentages of patients taking medication for hypertension (38% vs 36%) and hypercholesterolemia (32% vs 31%) were comparable between two groups ($p>0.05$ for all)

**Table-1:** Comparison of cardiovascular risk factors and bone mineral density in patients with and without aortic valve calcification.

| Variable | Patients with AVC (n=160) | Patients without AVC(n=425) | P value |
|---|---|---|---|
| Age,(year) | 66□ 10 | 57□ 10 | <0.001 |
| Female (%) | 63 (39%) | 150 (35%) | 0.36 |
| Body mass index | 26□ 3 | 27□ 4 | 0.008 |
| Smoking Status | 43 (27%) | 131 (31%) | 0.24 |
| Diabetes mellitus | 27 (17%) | 80 (19%) | 0.32 |
| Hypercholesterolemia | 57(36%) | 161 (38%) | 0.63 |
| Hypertension | 104 (65%) | 216 (52%) | <0.001 |
| Coronary Artery Disease | 102 (64%) | 233 (55%) | 0.027 |
| T score | -1.93□ 1.3 | -1.48□ 1.4 | <0.001 |

AVC: Aortic valve calcification

**Table-2.** Logistic regression analysis for aortic valve calcification

| Variable | Odds ratio | 95% CI | P value |
|---|---|---|---|
| Age (year) | 1.09 | 1.06-1.1 | 0.001 |
| Hypertension (Y vs N) | 1.7 | 1.2-2.8 | 0.004 |
| Body Mass Index | 0.95 | 0.89-1 | 0.048 |

Y indicates yes; and N, no; CI, confidence interval

***Coronary Artery Disease and AVC***

Presence of CAD was significantly higher in patients with AVC compared to those without AVC however it was not found to be associated with AVC (table-I, and II). There were no significant differences between the patients with and without AVC regarding the reasons for referral for coronary angiography. Angina was the leading indication in both patients with and without AVC (40% and 39% respectively), followed by myocardial infarction (33% vs. 35%), chest pain (27% vs. 26%) and there were not statistically significant differences between two groups (p>0.05 for all).

***Bone Mineral Density and AVC***

The prevalence of osteopenia was comparable in patients with and without AVC (60/160, 37% vs 157/425, 37%, p>0.05). Rate of osteoporosis was significantly higher in patients with AVC than in those without AVC (57/160, 36% vs 99/425, 23% p=0.001 respectively), where as rate of normal BMD was significantly high in patients without AVC compared to those with AVC (169/425, 40% vs 43/160, 27% p=0.001 respectively). Both Tscore and age-gender adjusted T score were not found to be associated with AVC (p=0.09, 0.011 respectively).

## DISCUSSION

There are two main findings of our study; [20] age and hypertension are positively associated with AVC and BMI is negatively and independently associated with AVC,[3] Although the BMD of patients with AVC are significantly lower than those without AVC. BMD has not found to be associated with AVC. Additionally, although the presence of CAD is significantly higher in patients with AVC compared to those without AVC, it was not found to be associated with AVC.

***Association of AVC with Cardiovascular Risk Factors and CAD***

Cardiovascular risk factors such as hypercholesterolemia, diabetes mellitus, hypertension, cigarette smoking, male sex, and age are reported to increase the incidence of AVC.[3-8] Aortic annular calcification has been reported to be related with systemic atherosclerosis.[21] Age and hypertension has been shown to be associated with AVC in most of the studies. In accordance with the literature we have found that age and hypertension are independently associated with AVC in patients with undergoing coronary angiography. Additionally BMI is found to be negatively associated with AVC. The Helsinki Aging Study showed that hypertension, age and a low BMI were independent predictors of AVS; however,

cholesterol, smoking and diabetes mellitus were not predictors.[7] In our previous study which had relatively small number of patients recruited from the echocardiography laboratory, we demonstrated that age and hypertension were independently associated with AVC. Although the mean height and weight of the patients with AVC were significantly lower then those of without AVC, it did not gain statistical significance on logistic regression analysis.[3]

In contrast to most of the studies evaluating the association between cardiac calcification and atherosclerosis, we have not demonstrated and association between AVC and CAD. Aronow et al[22] reported that older subjects with valvular aortic sclerosis have a higher prevalence of prior CAD and a higher risk (1.8 times) of new coronary events than older subjects without valvular aortic sclerosis, after controlling for the confounding effects of other prognostic variables. Adler et al[20] has reported that there is a significant association between AVC and significant coronary artery disease in patients undergoing coronary angiography.

On the other hand, absence of relation between AVC and CAD does not necessarily indicate the absence of the association between AVC and atherosclerosis. Definition of CAD may partly play a role in the controversial results. We defined CAD as >50% stenosis in epicardial coronary artery but in the Adler's report it was defined as >70% stenosis.[20] Patients having <50% or <70% stenosis still do have atherosclerosis in their coronary arteries. It could have been demonstrated by intravascular ultrasonography which we were not able to do.

### *Bone Mineral Density and AVC*

It has been reported that low BMD are often present in patients with vascular calcification,[12,13] and the composition of calcified plaque is similar to bone mineral hydroxyapatite, suggesting that the two conditions may be interrelated.[16] On the other hand, some authors have reported that osteoporosis is not associated with aortic calcification, suggesting that any association is due to chance alone.[14,15] However, it is not possible to make a head to head comparison between our study and published literatures. Studies indicating an association between low BMD and atherosclerosis are mostly population based epidemiologic or indirectly showing the relation either by with ultrasonography, or electron beam computerized tomography.[15,23-27] Those studies are mainly focused on vascular calcification not on the aortic valve calcification. On the other hand our study population consisted of patients who undergone coronary angiography. We focused on the calcification of the aortic valve not on the calcification of the aorta. These are the main differences of our study compared to those in literature. Diminishing of T score's statistical significance after adjusting for age and gender can be partly explained by the age dependency of both conditions. It has also been reported that osteoporosis and aortic calcification appears to be independent process that occur by aging.[17] On the contrary, our group has reported that T score is independently associated with AVC recently. However in that study patients were recruited from the echocardiography laboratory. The way of patient recruitment may also play a role for controversial results. Since most of the studies evaluating the possible association between vascular calcification and BMD are based on epidemiological data, the causal relationship is not known very well.

In conclusion we have demonstrated that age, hypertension, and BMI are independently associated with AVC. Age-gender adjusted T score measuring BMD is found to be independent of AVC. Although we have shown absence of association between CAD and AVC, this issue remains to be clarified in further clinical studies.

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