Can the Ratio of Calcium to Albumin Predict the Severity of Aortic Stenosis?

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ABSTRACT

Objective: Aortic sclerosis is observed in 25% of the elderly population, and 2.5% of these patients have severe aortic stenosis (AS). Numerous studies have reported a relationship between the serum calcium or albumin levels and AS. The present study investigated the relationship between the calcium to albumin ratio (CAR) and AS. Methods: Our study included 185 patients and 108 subjects as the control group. A routine transthoracic echocardiographic evaluation and laboratory examinations were performed in all participants. The corrected serum calcium levels were calculated using the most commonly used formula: corrected calcium=measured total calcium (mg/dL) + 0.8 (4.0−serum albumin [g/dL]). Results: The serum C-reactive protein CRP, calcium, and corrected calcium levels were significantly different between the study groups (p<0.05), and the albumin levels were significantly decreased parallel with the AS severity (p<0.001). Also, we detected a negative correlation between the albumin and corrected calcium levels and the EuroSCORE. CAR and corrected calcium to albumin ratio (cCAR) were significantly higher in the AS group, as expected (p<0.01). In the logistic regression analysis, albumin, CRP, low-density lipoprotein LDL, theCAR, and cCAR levels were found to be significantly and independently associated with the presence of AS (p<0.05). Moreover, in a regression analysis in the subgroup of AS only, albumin, the cCAR, and CAR were independently associated with the presence of very severe AS. Conclusion: Our study showed an important relationship between the CAR and AS. Therefore, in clinical practice, this simple, inexpensive, and practical method may predict the severity of AS. Keywords: Albumin, aortic stenosis, calcium, calcium to albumin ratio

INTRODUCTION

The best-known pathologies underlying aortic stenosis (AS) include aortic valve thickening and sclerosis, followed by progressive calcification causing obstruction. Aortic stenosis is observed in 25% of the elderly population (1), and changes on the cusp share similarities with the structure of atherosclerotic plaque (2). Approximately 2.5% of these patients face severe AS, along with progressive calcification (3). Within this progressive process, the changes in the valve include bone cells in the osteoblastic phenotype, and in advanced AS cases, bone structures showing a lamellar structure (4, 5).

A previous study found that low serum calcium levels were associated with increased calcium hydroxyapatite deposition in native aortic valves in patients with severe calcific AS (6). On the other hand, another study demonstrated that serum calcium levels were higher in patients with AS among subjects with normal renal function who did not have apparent atherosclerosis (7). In another study, while no significant relationship was detected between the severity of AS and serum calcium levels, it was reported that the increase in serum phosphate levels and the calcium-phosphate product levels have a negative relationship with the aortic valve area (AVA) (8). It has been previously shown that in patients with AS who underwent a transcatheter aortic valve implantation (TAVI) procedure, a low serum albumin level is an important prognostic factor for post-procedure mortality (9). Being an important marker of fragility, the serum albumin levels have been demonstrated to be lower in patients with AS, which is seen at an advanced age and in fragile patients (10). Additionally, inflammation has been demonstrated to play an active role in the progression of aortic sclerosis and calcific AS (11, 12). Also, albumin is known as a negative acute-phase reactant of which the blood level decreases during inflammation (13). Moreover, the most important transporter protein of calcium ions in the blood is albumin (14).

Our study explored the relationship of calcific AS with serum albumin, calcium, albumin-corrected calcium levels, and espe-
cially the ratio of two closely interacting molecules, calcium and albumin.

METHODS

Our study included 185 patients admitted to our clinic between January 2014 and January 2017, diagnosed with severe AS, and 108 subjects who were admitted to our cardiology clinic for examination purposes and for whom no obstructive coronary artery disease (CAD) was detected after non-invasive tests, including the exercise test, myocardial perfusion scintigraphy, and computerized tomographic angiography, and no valvular pathology was detected by echocardiography. Patients with a history of acute coronary syndrome within the past month; those with active malignancy; those who used immunosuppressive, steroid, or diuretic agents on regular basis, or external Vitamin D or calcium supplements; those who suffered from chronic renal disease or renal disease requiring hemodialysis; those with a clinical presentation of infective endocarditis; those who suffered from an acute or chronic connective tissue disease; those who had AS but with no available previous medical records; those who had primary hyperparathyroidism or inadequately treated thyroid issues; and those who had a clinical presentation of Stage 3-4 cardiac failure were excluded from the study. Our study was designed in accordance with the Declaration of Helsinki, and the local ethical committee of Yıldırım Beyazıt University approved the study protocol (Date: 05.03.2018, No: 56). All patients were informed about the aims and the protocol of the study, and written informed consent was obtained.

**Transthoracic Echocardiographic Evaluation**

All patients underwent the echocardiographical examination, and the left ventricular ejection fraction was calculated using the modified Simpson method. It was performed using a IE33 echocardiography system (Philips Medical Systems, Eindhoven, The Netherlands) with a 3.5 MHz transducer by two experienced operators. The parasternal short- and long-axis, apical four-chamber, and subcostal four-chamber views were used as standard echocardiography. The aortic jet velocity was calculated by Doppler echocardiography. The transvalvular pressure gradient was determined by the Bernoulli formula, and AVA was calculated by the continuity equation. AS was defined as mild if the mean systolic transaortic gradient was <25 mmHg or the jet velocity was <3.0 m/s, moderate if the mean systolic transaortic gradient was 25-40 mmHg or jet velocity was 3.0-4.0 m/s, severe if the mean systolic transaortic gradient was >40 mmHg or jet velocity was >4.0 m/s, and very severe if the jet velocity was greater than 5.0 m/sn (15, 16).

**Routine Laboratory Examinations**

After 12 h of the fasting period, the blood for routine hematologic and biochemical tests was collected. The serum levels of fasting plasma glucose, lipid parameters, creatinine, and the hematologic values were determined using the standard methods. The serum albumin and calcium levels were calculated using the COBAS INTEGRA Albumin Gen. 2/cobas c systems (Roche Diagnostics Corporation; Manheim, Germany). We used a reference range 3.5-5.2 g/dL and 8.8-10.2 mg/dL for albumin and calcium tests, respectively. The corrected serum calcium levels were calculated using the most commonly used formula in clinical practice, if the serum albumin level was <4 mg/dL: corrected calcium=measured total calcium (mg/dL) + 0.8 (4.0–serum albumin [g/dL]) (17).

**Statistical Analysis**

The data collected during the research were analyzed using the Statistical Package for the Social Sciences 15.0 statistical package program (SPSS Inc.; Chicago, IL, USA). Descriptive statistics were depicted as the mean±standard deviation or median (inter-quartile range) for continuous variables, and as the number of cases (n) and percentages (%) for categorical variables. The normality distribution was evaluated using the Kolmogorov-Smirnov test. Baseline characteristics were compared with the independent sample t-test, Mann-Whitney U test, chi-square test, or Fisher’s exact test (wherever applicable). Pearson and Spearman’s correlation test was used to assess the correlation between calcium, albumin, calcium/albumin ratio, and the mean systolic transaortic gradient and AVA. A logistic regression analysis was used to examine the association between AS, severe AS, and other variables. Variables with a p-value of <0.1 in a univariate logistic regression analysis were included in a multivariate logistic regression analysis model. A p-value <0.05 was considered to be statistically significant.

**RESULTS**

Clinical and demographic characteristics of the study groups are shown in Table 1. Hypertension and diabetes mellitus rates were higher, as expected, in the AS group (n=185) than in the control group (n=108), but there was no statistically significant difference in the subgroup between AS (n=145) and very severe AS group (n=40) (Table 2). The serum C-reactive protein (CRP), calcium, and corrected calcium levels were significantly different between the study groups (p<0.05), but only the serum CRP levels were still found to be significantly higher in the subgroup of AS (p=0.039). In addition, the albumin level was significantly decreased parallel with the severity of AS (4.49±0.51 in the control group, 3.90±0.34in the AS group, and 3.69±0.31 in the very severe AS group; p<0.001). There was a significant positive correlation between albumin and AVA (r=0.264, p<0.001). Moreover, we did not observe a positive or negative correlation between AVA and neither calcium nor corrected calcium (respectively, r=0.05, p=0.485; and r=−0.190, p=0.796). Also, we detected a negative, but weak correlation between the albumin and corrected calcium levels and the EuroSCORE (Figure 1).

In addition, the calcium to albumin ratio (CAR) and corrected calcium to albumin ratio (cCAR) were significantly higher in the AS group, as expected (p<0.01). Although the CAR and cCAR were detected as numerically higher in the very severe AS group than the AS group, they were statistically insignificant (respectively, p-value 0.548 and 0.341). Also, the cCAR was positively correlated with the CRP level (r=0.197, p=0.019) and negatively correlated with AVA (r=−0.168, p=0.023) (Figure 2).

To determine the possible confounding factors for AS, a logistic regression analysis was performed. In the logistic regression analysis, the albumin, CRP, low-density lipoprotein (LDL), CAR, and
cCAR were found to be significantly and independently associated with the presence of AS (p<0.05). Moreover, the regression analysis in the AS only subgroup showed that albumin (odds ratio OR, 6.134; 95% confidence interval CI, 1.967-19.136; p=0.001) and cCAR (OR, 4.613; 95% CI, 0.930-22.876; p=0.0470) and CAR (OR, 10.342; 95% CI, 1.252-24.296; p=0.030) were independently associated with the presence of very severe AS (Table 3).

**DISCUSSION**

The most important finding of our study is that AS is independently correlated with the CAR and albumin levels. To the best of our knowledge, this is the first large-scale study to investigate the association between the CAR and AS. We demonstrated that the CAR was significantly higher in patients with severe AS than in control subjects. Also, the CAR had a significantly positive correlation with CRP and negative correlation with AVA. Besides, we showed that the lower albumin levels and a higher CAR were also independently associated with the presence of very severe AS.

Aortic stenosis is a chronic disease that shares similarities with atherosclerotic CAD, such as mechanical stress, chronic inflammation, calcification, and lipid deposition on valvular leaflets (2, 18). Being a commonly used and an important marker of inflammation, it has been demonstrated that CRP levels are increased...
<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Group (n=108)</th>
<th>Aortic Stenosis (n=185)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, (years) (mean±std)</td>
<td>77.87±7.53</td>
<td>76.37±6.02</td>
<td>0.079</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>45 (41.6)</td>
<td>143 (77.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>10 (9.2)</td>
<td>59 (31.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine, mg/dL, mean±std</td>
<td>0.84±0.21</td>
<td>0.97±0.4</td>
<td>0.06</td>
</tr>
<tr>
<td>LDL-C, mg/dL, (median–IQR)</td>
<td>119 (37–236)</td>
<td>100 (31–358)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C, mg/dL, (median–IQR)</td>
<td>45 (23–80)</td>
<td>46 (12–103)</td>
<td>0.842</td>
</tr>
<tr>
<td>Triglyceride, mg/dL, mean±std</td>
<td>141 (34–584)</td>
<td>102 (30–511)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP, (median–IQR)</td>
<td>3.61 (0.8–16)</td>
<td>4.62 (1.1–37)</td>
<td>0.042</td>
</tr>
<tr>
<td>Calcium (mg/dL) (median–IQR)</td>
<td>9.0 (6.91–12.17)</td>
<td>9.52 (8.30–10.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cCalcium (mg/dL) (median–IQR)</td>
<td>9.19 (6.9–12.17)</td>
<td>9.52 (8.5–10.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin (gr/dL) (mean±std)</td>
<td>4.49±0.51</td>
<td>3.88±0.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium/albumin ratio</td>
<td>2.12±0.18</td>
<td>2.33±0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Corrected calcium/albumin ratio</td>
<td>2.12±0.19</td>
<td>2.38±0.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF, %, (mean±std)</td>
<td>61.46±4.64</td>
<td>53.07±14.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum gradient, mmHg</td>
<td>–</td>
<td>82 (36–187)</td>
<td>–</td>
</tr>
<tr>
<td>Mean gradient, mmHg</td>
<td>–</td>
<td>49 (20–114)</td>
<td>–</td>
</tr>
<tr>
<td>Aortic valve area (cm²), (median–IQR)</td>
<td>–</td>
<td>0.64 (0.30–1.0)</td>
<td>–</td>
</tr>
<tr>
<td>Logistic EuroSCORE (%)</td>
<td>–</td>
<td>16.54 (2.86–60)</td>
<td>–</td>
</tr>
<tr>
<td>Society of Thoracic Surgeons score (%)</td>
<td>–</td>
<td>5.7 (1.20–31.2)</td>
<td>–</td>
</tr>
</tbody>
</table>

CAD: coronary artery disease; cCalcium: corrected calcium; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction; WBC: white blood cell

Figure 2. a, b. Correlation analysis of (a) cCAR and CRP, and (b) cCAR and AVA
AVA: aortic valve area; CRP: C-reactive protein; cCAR: corrected calcium to albumin ratio
in patients with degenerative AS, such as atherosclerotic heart disease (19). A later study revealed that CRP levels measured at intervals in patients with asymptomatic AS played a prognostic role in the severity, progression, and clinical outcomes of the disease. In the same study, it was also reported that long-term survival rates are lower in AS characterized by high CRP levels (20).

Another important marker of chronic inflammation is albumin, which has been used in clinical practice in recent years as it shows the fragility of AS patients (9, 10). Serum albumin, a negative acute-phase protein, is insufficiently produced by the liver during inflammation (13). Several other studies established that low albumin levels were related to an increased risk of cardiovascular mortality and morbidity (21). In their study that included patients who underwent TAVI for AS, Yamamoto et al. (22) detected higher all-cause and cardiovascular mortality rates after the procedure and during their 1-year follow-up in individuals whose pre-procedure albumin value was <3.5 mg/dL. Another striking point in this study is that the log EuroScore and the The Society of Thoracic Surgery Risk Score STS were considerably higher in the group with low albumin levels. However, different from our study, the peak velocity and the mean aortic gradient were found to be higher in the group with high albumin levels, and the valvular area was observed to be comparable between both groups (22). In a study by Kofman et al. (23), while mean aortic gradients were found to be comparable in individuals with a low serum albumin level, AVA was found to be smaller in the group with a low albumin level. In their study, Bogdan et al. (9) have observed comparable mean and maximal aortic gradients and AVAs between the groups with low and high albumin levels. In our study, while the albumin level was negatively correlated with the mean and maximal aortic pressure, a positive correlation was observed with AVA. Recently, the Valve Academic Research Consortium committee has suggested adding the "fragility" status of patients to classical pre-operative risk factors in patients treated for AS (10, 24). A serum albumin level <3.5 g/dL has been accepted as a fragility indicator according to these criteria (10, 24).

Additionally, albumin is the most important transporter of calcium in the blood. Forty percent of calcium is transported as albuminbound. Therefore, for an exact assessment of the total calcium level in the blood, albumin levels should be also known.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Severe Aortic Stenosis (n=145)</th>
<th>Very Severe Aortic Stenosis (n=40)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, (years) (mean ±std)</td>
<td>77.68±7.47</td>
<td>78.55±7.78</td>
<td>0.532</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>110 (75.8)</td>
<td>33 (82.5)</td>
<td>0.254</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>13 (32.5)</td>
<td>46 (145)</td>
<td>0.534</td>
</tr>
<tr>
<td>Creatinine, mg/dl, (median–IQR)</td>
<td>0.93 (0.39–1.44)</td>
<td>0.89 (0.4–1.5)</td>
<td>0.351</td>
</tr>
<tr>
<td>LDL–C, mg/dl, (median–IQR)</td>
<td>98.58 (36.2–358)</td>
<td>103.10 (31.1–165)</td>
<td>0.644</td>
</tr>
<tr>
<td>HDL–C, mg/dl, (median–IQR)</td>
<td>46 (12–103)</td>
<td>47.5 (16–76)</td>
<td>0.765</td>
</tr>
<tr>
<td>Triglyceride, mg/dL, mean±std</td>
<td>102 (30–511)</td>
<td>99.5 (34–295)</td>
<td>0.999</td>
</tr>
<tr>
<td>CRP, (median–IQR)</td>
<td>4.3 (0.17–20)</td>
<td>5.79 (0.24–30)</td>
<td>0.039</td>
</tr>
<tr>
<td>Calcium (mg/dL) (median–IQR)</td>
<td>9 (7–12.17)</td>
<td>8.91 (6.91–11.36)</td>
<td>0.182</td>
</tr>
<tr>
<td>Albumin (gr/dL) (mean±std)</td>
<td>3.90±0.34</td>
<td>3.69±0.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium/albumin ratio (mean±std)</td>
<td>2.33±0.25</td>
<td>2.36±0.33</td>
<td>0.548</td>
</tr>
<tr>
<td>Corrected calcium/albumin ratio (mean±std)</td>
<td>2.37±0.28</td>
<td>2.43±0.40</td>
<td>0.341</td>
</tr>
<tr>
<td>LVEF, %, (mean±std)</td>
<td>51.35±15.38</td>
<td>59.30±6.41</td>
<td>0.002</td>
</tr>
<tr>
<td>Minimum gradient, mmHg</td>
<td>77 (36–105)</td>
<td>132.5 (87–187)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean gradient, mmHg</td>
<td>45 (20–64)</td>
<td>72 (58–114)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic valve area (cm²), (median–IQR)</td>
<td>0.66±0.15</td>
<td>0.47±0.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Logistic EuroSCORE (%)</td>
<td>21.57±15.43</td>
<td>21.77±13.61</td>
<td>0.944</td>
</tr>
<tr>
<td>Society of Thoracic Surgeons score (%)</td>
<td>7.12±4.73</td>
<td>6.24±3.38</td>
<td>0.271</td>
</tr>
</tbody>
</table>

CAD: coronary artery disease; cCalcium: corrected calcium; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction; WBC: white blood cell
Furthermore, a study in patients who used a calcium channel blocker revealed that serum calcium levels showed a trend toward being higher, while serum phosphate levels were not studied may be considered as a drawback. Moreover, the fact that only one serum level was used, and that other inflammation markers (interleukins, fibrinogen, etc.) were not studied may also be considered as a limitation. Consequently, the CAR that emerged as a novel parameter can be calculated using simple biochemistry tests in daily practice and could benefit other techniques for determining the severity of AS. We also detected its correlation with the CAR and the severity of AS. We also detected its correlation with CRP and that it was an important inflammation marker.

Our study has a few limitations. First, it is a single-center study with a retrospective design. The fact that Vitamin D and PTH levels, which are known to have an effect on calcium metabolism, were not studied in patient groups is an important drawback. Another important limitation is the low number of patients included into the study and the lack of patients with mild and moderate AS. Also, the fact that serum calcium phosphate levels and phosphate levels were not studied may be considered as a drawback. Furthermore, the fact that only one serum level was studied in patients, that the mean of work-ups within the year was not used, and that other inflammation markers (interleukins, fibrinogen, etc.) were not studied may also be considered as limitation.

Table 3. Logistic regression analysis of predictive factors for very severe aortic valve stenosis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio (OR)</th>
<th>95% Confidence Interval for OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/dL)</td>
<td>1.315</td>
<td>0.833-2.075</td>
<td>0.240</td>
</tr>
<tr>
<td>cCalcium (mg/dL)</td>
<td>1.321</td>
<td>27.065-219.1</td>
<td>0.224</td>
</tr>
<tr>
<td>Albumin (gr/dL)</td>
<td>2.263</td>
<td>1.180-4.233</td>
<td>0.016</td>
</tr>
<tr>
<td>Corrected calcium/albmin ratio</td>
<td>0.010</td>
<td>0.002-0.049</td>
<td>0.001</td>
</tr>
<tr>
<td>Calcium/albmin ratio</td>
<td>0.011</td>
<td>0.003-0.051</td>
<td>0.001</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.991</td>
<td>0.899-1.093</td>
<td>0.042</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>1.013</td>
<td>1.005-1.021</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Logistic regression analysis of predictive factors for very severe aortic valve stenosis in patients with severe aortic stenosis

CONCLUSION

The present study detected an important relationship between the CAR and the severity of AS. We also detected its correlation with CRP and that it was an important inflammation marker. Consequently, the CAR that emerged as a novel parameter can be calculated using simple biochemistry tests in daily practice and could benefit other techniques for determining the severity of AS. Larger studies on this subject are needed.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Yıldırım Beyazıt University (Date: 05.03.2018, No: 56).

Informed Consent: Written informed consent was obtained from patients who participated in this study.
Task Force on Practice Guidelines. Jam Coll Cardiol 2014; 63: 2438-88. [CrossRef]


