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Role of calcium–albumin ratio in severity of coronary artery disease assessed by angiographic SYNTAX score

Anjiyografik SYNTAX skoru ile değerlendirilen koroner arter hastalığı ciddiyetinde kalsiyum-albumin oranının rolü

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Abstract

Aim: Numerous studies have reported a relationship between serum calcium or albumin levels and acute coronary syndromes and coronary artery disease. The present study investigated the relation between serum albumin, calcium or albumin-corrected calcium levels or calcium/albumin ratio (CAR) and extensiveness and severity of atherosclerosis.

Methods: This prospective study included patients with non-ST elevation myocardial infarction (NSTEMI, n=120) and a control group (n=109). We used the SYNTAX score to evaluate the association between CAR and severity and extent of coronary artery disease.

Results: There were higher, but statistically nonsignificant, levels of calcium in patients with NSTEMI (p=0.058). However, serum albumin-corrected calcium levels were significantly higher in NSTEMI group (p=0.001). Yet, albumin levels did not differ between the groups (p=0.093). CAR and corrected calcium–albumin ratio (cCAR) were significantly higher in NSTEMI group (p=0.001). A positive correlation existed between CAR (r=0.235, p=0.010), cCAR (r=0.259, p=0.004), and SYNTAX score, whereas albumin and SYNTAX score (r=−0.259, p=0.004) showed a negative correlation.

Conclusion: Calcium/albumin ratio has been found to be associated with an increased coronary atherosclerotic burden as calculated by SYNTAX score. Further large-scale studies are warranted to confirm our findings.

Keywords: Non-ST elevation acute myocardial infarction, SYNTAX score, calcium-albumin ratio

Öz

Amaç: Serum kalsiyum ve albumin seviyeleri ile akut koroner sendromlar ve koroner arter hastalığı arasındaki ilişki birçok çalışmada gösterilmiştir. Sunulan çalışmada, serum albumin, kalsiyum, albumin-düzeltilmiş kalsiyum seviyeleri ve kalsiyum/albumin oranı (KAO) ile aterosklerozun yaygınlık ve ciddiyetinin ilişkisi araştırılmıştır.

Yöntemler: Bu prospektif çalışmaya non-ST elevasyonlu miyokard infarktüsü olan hastalar (NSTEMI, n=120) ve kontrol grubu (n=109) dahil edildi. KAO ile koroner arter hastalığı yaygınlık ve ciddiyetinin ilişkisini değerlendirmek için SYNTAX skoru kullanıldı.

Bulgular: NSTEMI hastalarında istatistiksel anlamlı olmadan daha yüksek kalsiyum seviyeleri vardı (p=0.058). Buna rağmen serum albumin-düzeltilmiş kalsiyum seviyeleri istatistiksel anlamlı olarak NSTEMI grubunda daha yüksekti (p=0.001). Albumin seviyeleri ise gruplar arasında farklılık göstermedi (p=0.093). KAO ve düzeltilmiş kalsiyum/albumin oranı (dKAO), NSTEMI grubunda anlamlı olarak daha yüksekti (p=0.001). KAO (r=0.235, p=0.010) ve dKAO (r=0.259, p=0.004) ile SYNTAX skoru arasında pozitif korelasyon mevcut iken, albumin ile SYNTAX skoru (r=−0.259, p=0.004) arasında negatif korelasyon görüldü.

Sonuç: Kalsiyum/albumin oranı, SYNTAX skoru ile hesaplanan artmış koroner aterosklerotik yük ile ilişkili bulunmuştur. Bulgularımızı doğrulamak için daha geniş çaplı çalışmalar gereklidir.

Anahtar kelimeler: Non-ST elevasyonlu akut miyokard infarktüsü, SYNTAX skoru, kalsiyum-albumin oranı

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Introduction

Increasing incidences of atherosclerotic cardiovascular diseases have become a growing source of global disease burden, thereby leading to a significant rise in global morbidity and mortality [1]. Medical professionals, with a keen interest in the subject, have been working on several different scoring systems and laboratory parameters to obtain an estimate of the prognosis and severity of the disease. The SYNTAX score is one of the most widely used angiographic grading tools for determining the complexity and severity of coronary artery disease (CAD). Many earlier studies demonstrate a higher SYNTAX score as an independent predictor of cardiovascular mortality and morbidity in patients with acute coronary syndromes (ACS) [2-4]. A recent, large-scale study estimated the levels of serum albumin in patients with ACS to be inversely proportional to the SYNTAX score and in-hospital mortality [5]. Moreover, various studies report hypoalbuminemia not only to be a predictive marker for an increased risk of developing CAD, but also a prognostic factor for heart failure, stroke, and myocardial infarction [6-8]. Several studies have hypothesized different mechanisms for the effect of albumin on the atherosclerotic cardiovascular disease. At the first place, ACS that represent an inflammatory process are accompanied by changes in albumin, a negative acute-phase reactant [9, 10]. Secondly, albumin has been found to inhibit the activation and aggregation of platelets [11]. It acts as a specific inhibitor of human endothelial apoptosis and serves as a major antioxidant in serum, where it plays a crucial role in ligand binding and free-radical trapping [12, 13]. In addition, albumin is the major binding protein for calcium, which has a significant role in cardiovascular diseases, including platelet activation, coagulation, and cardiac contraction. In short, calcium is found in three different forms in the plasma: (1) as free or ionized form, which is the physiologically important form (50%), (2) linked to albumin (40%), and (3) as a soluble complex (10%) [14]. Thus, it can be speculated that the levels of serum calcium and albumin are interrelated. Therefore, the level of calcium can not be estimated without evaluating the level of serum albumin during a laboratory test. The lower levels of calcium reported in patients with ST-elevation myocardial infarction (STEMI), like serum albumin levels, are considered to be a predictive factor for in-hospital mortality [15]. In another study, authors reported similar findings and suggested that inclusion of serum calcium in the GRACE (Global Registry of Acute Coronary Events) scoring system may further help in the more precise prediction of the risk [16]. Though many studies have demonstrated an inverse relationship between serum calcium or albumin levels and ACS and CAD, a few have also shown a positive relationship between these factors. Contrary to above, some studies report no relationship between these players [17-21]. Therefore, the dilemma whether serum calcium and albumin levels are risk factors for CAD persists.

The current study investigated the relationship between serum albumin, calcium or albumin-corrected calcium levels and especially, two interdependent variables, calcium to albumin ratio (CAR), and the extensiveness and severity of atherosclerosis in CAD.

Material and methods

Study Population

This study was designed in a prospective case-control manner. The local ethical committee approved the experimental protocol Yıldırım Beyazıt University Ethical Committee with a number of 82/2015 with confirmation of Helsinki declaration. All patients were informed about the aims and protocol of the study and written informed consent was obtained.

The study population consisted of 120 patients, with non-ST elevation myocardial infarction (NSTEMI), consecutively admitted to Atatürk Research and Training Hospital from January till December 2016 and 109 healthy subjects with a normal coronary angiography, normal treadmill stress test, myocardial perfusion scintigraphy or dobutamine stress echocardiography. The latter served as the control group. Patients with chronic severe renal or liver diseases, any disease of parathyroid glands, known calcium homeostasis disorders, hematologic disorders, an active malignancy, acute or chronic inflammatory disease and patients on thyroid replacement or immunosuppressive or hormone replacement therapy and who were administered drugs that affect bone or calcium metabolism, such as diuretics, corticosteroids, calcium or vitamin D supplements were excluded from the study. Hypertension was defined as repeated blood pressure measurements >140/90 mm Hg or history of a treatment with antihypertensive drugs. Diabetes mellitus was defined as fasting blood glucose >126 mg/dL, blood glucose >200 mg/dL at any time, or any patient treated with diet, oral medications, or insulin. Patients were designated as ‘‘current smokers’’ if they reported a history of active smoking in the last 6 months. Coronary angiography was performed for all patients who presented with NSTEMI. For the calculation of SYNTAX score, all coronary lesions causing ≥ 50% stenosis in vessels with a diameter of more than 1.5 mm were included. The SYNTAX score was calculated as per the latest online version of the software available on the website (http://www.SYNTAXscore.com). Different parameters were used for the calculation of the score including coronary dominance, number of lesions, segments included per lesion, the presence of total occlusion, bifurcation, trifurcation, aorto-ostial lesion, severe tortuosity, calcification, thrombus, diffuse/small vessel disease, and lesions measuring >20 mm. Individual SYNTAX scores using patient characteristics were analyzed by two to three experienced interventional cardiologists who were blinded for the study protocol. Patients were divided into 2 groups based on the SYNTAX score as high (≥ 23) or low score (<23) [2]. All patients underwent echocardiographical examination, and the left ventricular ejection fraction was calculated using the modified Simpson method [22].

Laboratory examinations

After 12 hour of fasting period, blood samples for hematologic and biochemical tests were collected. Serum albumin and calcium levels were analyzed at the first contact in the emergency room. Serum levels of fasting plasma glucose, lipid parameters, creatinine, and hematological values were determined using the standard methods. The serum high sensitive troponin T (hs-TnT) levels were measured using the Elecsys® Troponin T-high sensitive systems with a reference range of 3 to 14 pg/mL (Roche Diagnostics Corporation; Manheim, Germany). 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 of 3.5 to 5.2 g/dL and 8.8 to 10.2 mg/dL for albumin and calcium tests, respectively. The corrected serum calcium levels (cCalcium) were calculated using the most commonly used formula in clinical practice: Corrected calcium= measured total calcium (mg/dL) + 0.8 (4.0 − serum albumin [g/dL]) [23]. By using cCalcium levels, corrected calcium to albumin ratio (cCAR) was also calculated.

Statistical Analysis

The data collected during the research were analyzed using the SPSS 15.0 statistical package program (SPSS Inc., Chicago, IL, United States). Descriptive statistics were depicted

as mean ±standard deviation or median (inter-quartile range [IQR]) for continuous variables, and as the number of cases (n) and percentages (%) for categorical variables. 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). Spearman's correlation test was used to assess the correlation between calcium, albumin, CAR, and the SYNTAX score. The independent predictors of a high SYNTAX score were determined using the logistic regression analysis, which was performed as a multivariate analysis on parameters with statistically significant ($p<0.05$) differences as observed in univariate analysis. A p value less than 0.05 was considered to be statistically significant.

Results

The demographic features and laboratory parameters of the study population are shown in Table 1.

Table 1: Baseline clinical characteristics and laboratory parameters of the study population.

Variables	NSTEMI group (n=120)	Control group (n=109)	p
Age (years)¥	59.96 ±12.07	57.73 ±10.5	0.139
Hypertensionβ	67 (55.80)	57 (52.29)	0.343
Diabetesβ	35 (29.20)	30 (27.52)	0.449
Smokingβ	62 (51.66)	47 (43.11)	0.069
Fasting blood glucose (mg/dL)µ	116.50 (99–166)	93 (87–107)	0.001
eGFR (mL/min)µ	78 (48–110)	81(48–114)	0.543
Creatinin (mg/dl) ¥	1.1±0.31	0.9±0.22	0.041
Total cholesterol (mg/dL)¥	188.58 ±40.70	199.94 ±41.18	0.037
HDL (mg/dL)µ	40 (32.50–49)	45 (36–55)	0.002
LDL (mg/dL)µ	110.92 ±33.84	121.91 ±34.97	0.016
TG (mg/dL)µ	133 (82–196.50)	134 (101–187)	0.518
WBC (/mL)µ	8.39 (6.80–10.10)	7.60 (6.40–9.28)	0.006
Platelet × 1000 K/uLµ	217.50 (176.50–261)	257 (220–312)	0.001
MPV (fL)µ	9.30 (8.50–10.30)	10.60 (10.10–11.50)	0.001
hsTroponin T (pg/mL)µ	29 (8–162.5)	0.07 (0.01–0.15)	0.001
CK-MB (ng/mL)µ	2.90 (1.80–8)	-	-
LVEF (%)µ	60 (45–65)	65 (55–65)	0.001
Calcium (mg/dL)µ	9.60 (9.30–9.80)	9.51 (9.15–9.73)	0.058
cCalcium (mg/dL)µ	9.25 (9.06–9.52)	9.10 (8.82–9.28)	0.001
Albumin (gr/dL)µ	4.40 (4.17–4.60)	4.49 (4.20–4.67)	0.093
Calcium Albumin Ratioµ	2.19 (2.10–2.30)	2.11 (2.01–2.24)	0.001
cCalcium Albumin Ratioµ	2.10 (2–2.26)	2.01 (1.91–2.19)	0.001
SYNTAX score¥	9.19 ±9.72	-	-

¥: mean ± standard deviation, β: n (%), µ: median-IQR
NSTEMI: non-ST elevation myocardial infarction, GFR: Glomerular filtration rate, HDL: high-density lipoprotein cholesterol, hs: high sensitive, LDL: low-density lipoprotein cholesterol, TG: triglyceride, WBC: white blood cell, MPV: mean platelet volume, LVEF: left ventricular ejection fraction, CK-MB: creatinine kinase-myocardial band, IQR: interquartile range.

The mean age of the study population (n=229) was 59.01 ±11.35 years. Diabetes mellitus, hypertension, and smoking were reported to be more common in NSTEMI group, but not statistically significant. On the contrary, the levels of fasting blood glucose (p=0.001), creatinine (p=0.041), white blood cell (p=0.006), and high-sensitive cardiac troponin (hsTnT) (p=0.001) were significantly higher in patients belonging to NSTEMI group, as compared to control group. Among calcium and albumin serum levels, those of calcium were higher, but not statistically significant, in NSTEMI group (p= 0.058), whereas serum albumin-corrected calcium levels were statistically significantly higher in NSTEMI group (p=0.001). However, albumin levels did not differ between the groups (p= 0.093). Though CAR and cCAR were significantly higher in NSTEMI group, cCAR was found to be statistically more significant than CAR (p=0.001 and p=0.001, respectively). Median SYNTAX score was found to be 7 (IQR: 0–14) in NSTEMI group. CAR and cCAR demonstrated statistical difference among the subgroups with patients having a SYNTAX score < 23 (n=104) and ≥ 23 (n= 16, p= 0.048). Furthermore, as per the correlation analysis, the relationship between calcium, corrected calcium, and SYNTAX score (p=0.083 and p=0.504, respectively) was found to be non-significant. CAR (r=0.235, p=0.010), cCAR (r=0.259, p=0.004), and SYNTAX score were found to be positively correlated, whereas albumin and SYNTAX score (r=−0.259, p=0.004) displayed a negative correlation (Figure 1, 2). Univariate logistic regression analysis depicted albumin, cCalcium, CAR, cCAR, age, and ejection fraction to be significantly associated with a higher SYNTAX score (Table 2).

However, the multivariate regression analysis predicted only ejection fraction to be an independent predictor for high SYNTAX scores (p=0.001).

Table 2: Logistic regression analysis to determine the highest SYNTAX score.

Variables	Univariate Model				Multivariate Model			
	OR	95% CI		p	OR	95% CI		p
		Lower	Upper			Lower	Upper	
Age	1.092	1.035	1.152	0.001				
LVEF	0.874	0.815	0.937	0.001	0.866	0.797	0.924	0.001
HDL	1.022	0.990	1.054	0.177				
Hypertension	1.153	0.685	1.941	0.591				
Diabetes mellitus	1.136	0.637	2.027	0.549				
Albumin	0.103	0.025	0.430	0.002				
cCalcium	1.340	1.020	1.760	0.035				
Calcium albumin ratio	1.210	1.080	1.360	0.001				
cCalcium albumin ratio	1.022	1.012	1.033	0.001				

CI: Confident interval, LVEF: left ventricular ejection fraction, HDL: high density lipoprotein cholesterol, cCalcium: corrected calcium

Discussion

The current study established the presence of higher levels of serum calcium, corrected calcium levels and CAR in patients with NSTEMI than the healthy subjects. Also, this ratio was found to be associated with an increased coronary atherosclerotic burden as calculated by SYNTAX score. A significant correlation was reported between erum calcium and cCalcium levels and albumin ratio and SYNTAX score; however, the multivariate logistic regression model revealed CAR and cCAR not to be independent predictor factors for a high SYNTAX score. This study failed to demonstrate a positive or negative association between calcium and albumin levels in the patients with NSTEMI and those in control group.

The development and progression of atherosclerosis occur by endothelial dysfunction, platelet activation, oxidative stress, and inflammation, which are well-known mechanisms for atherosclerosis [24, 25]. Several studies have been conducted to investigate the effect of novel inflammatory markers on the relationship between inflammation and atherosclerosis during the

past decade. These findings indicated inflammation to play a significant role throughout the atherosclerotic process right from

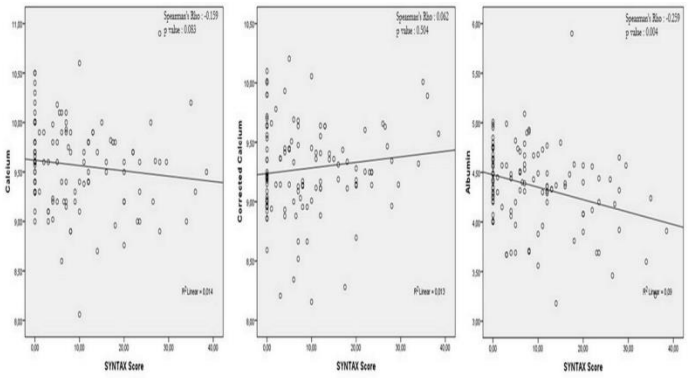

Figure 1. Correlation analysis with calcium, corrected calcium, albumin levels and SYNTAX score.

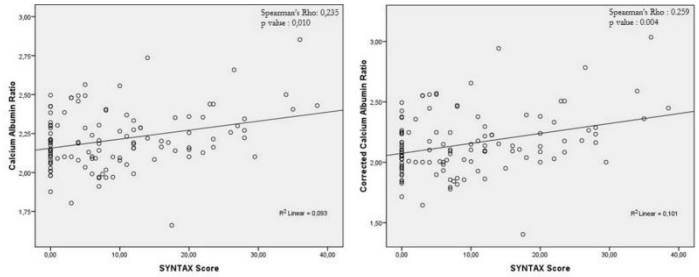

Figure 2. Correlation analysis with calcium albumin ratio, corrected calcium albumin ratio, and SYNTAX score.

the initiation to progression, activation of plaque, development of ACS as well as in the expansion of infarction [10, 26, 27]. Serum albumin, a negative acute-phase protein, is insufficiently produced by the liver during inflammation [28]. Similarly, several other studies have established low levels of albumin to be related to an increased risk of cardiovascular mortality and morbidity [29, 30]. Oduncu et al. [31] confirmed that low levels of serum albumin in patients admitted with NSTEMI were associated with a poor post-procedural myocardial reperfusion, a poor post-procedural left ventricular ejection fraction as well as complications related to infarct. They also found lower levels of serum albumin to be related to a higher cardiac and non-cardiac mortality, complex heart failure, stroke, and re-infarction during a long-term follow-up period (40 months). In another study, Celik et al. [32] demonstrated a lower serum albumin level, on admission, to be related to the development of restenosis in patients with bare-metal stents. On the other hand, studies exist that indicate lower serum albumin levels not to be associated with an increase in the probability of prevalent carotid atherosclerosis, both in males and females [19]. The present study reported a lower, although statistically nonsignificant, serum albumin level in the NSTEMI group. The finding could be attributed to following mechanisms: (1) Since the average age of the patients included in the study was low, a lower rate of chronic malnutrition or comorbid diseases could be anticipated. (2) Rigid inclusion criteria of the study might have influenced the results. (3) Inflammation is a well-known cause of atherosclerosis. As a high SYNTAX score is associated with the extent and severity of atherosclerosis, the lower intensity of inflammation in our study population could be explained by the lower average SYNTAX score (median=7) in NSTEMI group. These factors must have avoided the decrease of serum albumin concentration to statistically significant rates. As albumin is the major binding protein for calcium, several albumin-based standardization formulas have been recommended for the calculation of serum calcium levels. Recently published studies have demonstrated hypocalcemia to be a predictor of increased in-hospital mortality in patients with severe CAD [15, 16]. However, other studies have reported a high serum calcium concentration to be an independent predictor of incidence of CAD [33]. Also, a close association is known to exist between the serum calcium levels and traditional cardiovascular risk factors, such as hyperlipidemia, hypertension, and hyperglycemia [34, 35]. Another previously published study confirmed a significant linear relation between serum calcium level and blood pressure and the level of triglycerides. The same study also proved the level of cholesterol to increase with an elevation in the serum calcium levels [35]. Furthermore, serum calcium levels are higher in non–insulin dependent diabetes mellitus [36]. In the present study, though higher serum calcium levels were found in NSTEMI group than in control group, these were not statistically significant. In addition, serum albumin-corrected calcium level was significantly higher in NSTEMI group. It has been demonstrated that elevated calcium levels and the higher calcium/albumin ratio, emerged as a novel parameter, were strongly associated with all-cause mortality in patients with stable CAD [37]. It can be assumed that the results of this study support our findings. But, we need more data to confirm the association between all cause mortality and CAR in patients with NSTEMI.

Since the association between the levels of both serum calcium and albumin and atherosclerotic cardiovascular diseases is still in debate and has been shown to be positively correlated, we hypothesize that a higher calcium or cCAR may reflect their association with the presence and extensiveness of CAD more accurately than albumin and calcium alone. Given that the metabolism of albumin and calcium is closely related to each other, their ratio may predict the outcome of CAD more accurately. One of the mechanisms of action of albumin on the development of CAD could be its influence on calcium metabolism. To conclude, we believe that better and efficient results on the association between CAD and serum calcium could be obtained by the estimation of albumin-corrected calcium levels.

The most significant limitation of the present study was the insufficient sample size. Besides, data obtained did not allow us to evaluate the prognostic value of CAR or cCAR on adverse cardiovascular outcomes. Furthermore, the study lacked the comparison of CAR or cCAR with other inflammatory markers, such as CRP, hsCRP, fibrinogen, or IL 6, owing to the retrospective design of the study. Another important lack in the study was that all of the control group was not selected from patients with normal coronary arteries after coronary angiography. A low number of patients with a SYNTAX score of over 22 might have also reduced the strength of the study. And lastly, the analysis did not include concomitant medications of patients and serum levels of vitamin D or parathyroid hormone levels.

In conclusion, the present study is the first of its kind to demonstrate the relation between CAR or cCAR and atherosclerotic CAD. There is a need for an easily accessible and cost-effective biomarker to determine the disease activity in patients with atherosclerosis. In this context, the results of the study are clinically significant owing to the easily available estimation of CAR/cCAR, wider use, and being a relatively economical method for the determination of inflammatory status of body when compared to most other inflammatory markers. Further large-scale studies and investigations are warranted to authenticate the findings of this study on the atherogenic role of CAR/cCAR.

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