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# The relationship between obesity and coronary artery ectasia in patients presenting with acute coronary syndromes

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## Abstract

**Aim:** Obesity is a global health burden with an increasing worldwide incidence. Coronary artery ectasia (CAE) is frequently associated with obstructive coronary artery disease and acute coronary syndrome (ACS). Obesity and CAE are risk factors for ACS. Considering this linkage, we aimed to investigate the role of obesity in presence of CAE in patients presenting with ACS.

**Materials and Methods:** Patients hospitalized with a diagnosis of ACS in our tertiary center between January 2015 and May 2020 were included in this retrospective, case-control study. The patients presenting with ACS involving a coronary artery ectasia segment formed 'CAE group'. On the other hand, patients who were undergone coronary angiography with a diagnosis of ACS without coronary ectasia formed 'control group'.

**Results:** There were a total of 274 patients. Patients who were presented with ACS involving a CAE segment were in higher body mass index (BMI) tertials and BMI was an independent predictor for presence of CAE in patients presenting with ACS. Additionally advanced age, diabetes mellitus, hypertension, current smoking, increased neutrophil/lymphocyte ratio, higher fasting blood glucose, triglyceride and lower high-density lipoprotein (HDL) levels were found as independent risk factors for presence of CAE in patients presenting with ACS.

**Conclusion:** We detected obesity (being overweight or obese) as an independent risk factor associated with the presence of CAE in patients presenting with ACS. Higher triglyceride and fasting blood glucose and lower HDL levels detected in our study support the idea that metabolic syndrome plays a role and insulin resistance is the underlying mechanism for CAE presence in patients presenting with ACS.



## Introduction

Obesity is a global health burden with an increasing worldwide incidence. Thirty-nine to 49% of the global population above 18 years of age are overweight (OW) or obese according to GBD (Global Burden of Disease) Obesity Collaborators data [1]. The linkages between obesity and cardiovascular diseases such as acute coronary syndrome, coronary artery disease, heart failure, cardiac arrhythmias, and sudden cardiac death have been shown [2-6]. Besides, the relation between obesity and diabetes mellitus (DM), hypertension (HT), dyslipidemias and sleep apnea syndrome may also end-up with increased cardiovascular disorders [7]. The phagocytosis of cholesterol esters by foam cells and deposition inside the arterial wall initiates atherosclerosis with the thickening of the arterial intima. Insulin resistance, endothelial dysfunction, hyperinsulinemia and elevated proinflammatory and prothrombotic factor levels were shown to be increased in OW and obese patients resulting with accelerated atherosclerosis [8-10].

Coronary artery ectasia (CAE) is defined as the localized or diffuse dilatation of coronary artery segment >1.5 times relative to contiguous healthy segment [11,12]. Its incidence ranges between 0.22 – 5% according to angiographic and pre- and post-mortem studies, respectively [13,14]. Atherosclerosis is the most common underlying etiology (50-60%), with predominance in males while congenital, inflammatory and connective tissue diseases are the other important etiologic disorders [15]. Elevated elastase and collagenase activity in response to the inflammatory process may contribute to the formation of vascular ectasia in the presence of atherosclerosis. On the other hand, arterial hypertension, smoking, herbicides and cocaine consumption are among the reported risk factors for CAE. More than 80% of ectasia is associated with obstructive coronary artery disease. It may cause myocardial ischemia and

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acute coronary syndrome since coronary vasospasm, slow coronary flow and thrombus formation are the pathological and facilitating factors associated with CAE [16,17]. As a result, it is relevant to define related risk factors.

Obesity and CAE are risk factors for ACS. Considering this relation, we aimed to investigate the linkage between obesity and CAE in patients presenting with ACS.

## Materials and Methods

Patients hospitalized with a diagnosis of ACS in our tertiary center between January 2015 and May 2020 were included in this retrospective, case-control study. ST elevation myocardial infarction (STEMI), unstable angina pectoris (USAP), and non-ST elevation myocardial infarction (NSTEMI) were defined and treated according to recent guidelines [18,19]. Demographic, clinical and laboratory parameters were retrieved from hospital database and patients' files. Presence of stenosis ≥50% in two or more epicardial coronary arteries are defined as multivessel disease. Patients with end-stage hepatic failure, end-stage renal disease (glomerular filtration rate <30 mL/min/1.73m$^2$ or on dialysis), acute inflammatory disease, chronic infectious disease, collagen tissue diseases and malignancy were excluded.

The patients presenting with ACS involving a coronary artery ectasia segment formed 'CAE group'. On the other hand, patients who were undergone coronary angiography with a diagnosis of ACS without coronary ectasia formed 'control group' with a 1:1 randomization ratio. Coronary angiography was performed using the Judkins technique via femoral artery access. Two experienced interventional cardiologists, blinded to the patient's clinical data, analyzed all participants' angiographic images. Coronary artery stenosis greater than 50% in at least one coronary artery was considered as coronary artery disease (CAD) [20]. The number and distribution of coronary vessels affected by ectasia were determined using the Markis classification: type 1 = diffuse ectasia in two or three vessels; type 2 = diffuse ectasia in one vessel and focal ectasia in the rest of the vessels; type 3 = diffuse ectasia in one vessel; and type 4 = focal or segmental ectasia in one vessel [11]. Markis types 1, 2, and 3 are classified as diffuse ectasia and type 4 is classified as focal ectasia. Coronary angiography recodings were reviewed by two cardiologists blinded to each other. Body mass index (BMI) was calculated as weight (kg) ratio to height squared (m$^2$). An adult is considered normal weight if the BMI is 18.5 to <25 kg/m$^2$, overweight if the BMI is 25.0 to 29.9 kg/m$^2$, and obese if the BMI is ≥30.0 kg/m$^2$.

Chronic obstructive pulmonary disease (COPD) [21], cerebrovascular accident (CVA) [22], heart failure (HF) [23], myocardial infarction (MI) [24, hypertension (HT) [25] and diabetes mellitus (DM) [26], chronic kidney disease (CKD) [27] were described according to the established definitions. Transthoracic echocardiography was performed in all patients (Vivid S70; GE Medical System, Horten,Norway) and left ventricular ejection fraction were measured using Simpson's method.

The primary endpoint of the study was to define the linkage between obesity and CAE in patients presenting with ACS. The study protocol was approved by the Bagcilar Training and Research Hospital KAEK in agreement with the Declaration of Helsinki (2022/11/08/029).

### *Statistical analysis*

Statistical analyses were conducted with a commercially available software package (SPSS version 16.0, SPSS, Chicago, IL). Sample size was determined by power analysis and non-probability sampling technique. Data are expressed as mean ± SD for continuous variables and as counts and percentages for categorical variables. Differences were considered statistically significant if $p<0.05$. Normal distribution was analyzed with the Kolmogorov Smirnov test. Homogeneity of variance was calculated with the Levene test and the Lilliefors significance correction test. Student's t-test or its nonparametric counterpart Mann - Whitney U tests were used to analyze the differences between continuous variables, Chi-square and Fischer's exact tests were performed to analyze categorical variables. One-way analysis of variance (ANOVA) and its nonparametric counterpart Kruskal-Wallis tests were used. Post Hoc analysis was done with either Tukey HSD or Games-Howell tests. Variables having linear correlation were evaluated by using Pearson's correlation test and nonlinear variables were evaluated by using Spearman's correlation test. Univariate and multivariate logistic regression analysis were used to identify independent variables associated with presence of CAE in ACS. Receiver operating characteristic (ROC) curve analyses were performed to evaluate diagnostic accuracy of BMI for presence of CAE in patients presenting with ACS.

## Results

There were a total of 274 patients. Mean age was 59.1±9.3 and 72.6% was male. 71 patients (25.9%) had ectasia in left anterior descending coronary artery, 72 patients (26.3%) had ectasia in circumflex coronary artery, and 88 patients (32.1%) had ectasia in right coronary artery. Both groups were similar regarding subtypes of ACS (36% were STEMI whereas 64% were NSTEMI and USAP) and gender, previous CVA, history of CAD, COPD, CKD, atrial fibrillation and malignancy, and left ventricular ejection fraction. Age (60.5±10.8 vs. 57.5±7.3; p=0.007), BMI (30.8±3.4 vs. 25.3±4.4; p<0.0001), HT (58.4% vs. 44.5%, p=0.022), DM (67.9% vs. 37.2%, p<0.0001), HF (7.3% vs. 3.6%; p<0.0001), and smoking (50.4% vs. 28.5%, p<0.0001) were significantly higher in CAE group. Regarding plasma lipid profile serum total cholesterol (221.1±41.1 vs. 180.8±40.4; p<0.0001), triglyceride (210.3±58.9 vs. 104.9±36.4; p<0.0001) levels were significantly higher and high-density lipoprotein (HDL) cholesterol (36.1±6.7 vs. 50.5±10.6; p<0.0001) level was significantly lower in CAE group as compared to control group. Furthermore, serum creatinine (0.9±0.3 vs. 0.7±0.2; p=0.010), fasting blood glucose level (107.4±12.1 vs. 93.7±9.6; p<0.0001) and neutrophil to lymphocyte ratio (NLr) (4.8±1.9 vs. 3.7±0.5; p<0.0001) were significantly higher and glomerular filtration rate (GFR) (88.1±19.9 vs. 93.8±13.1; p=0.041) was lower in CAE patients presenting with ACS. All demographical, clinical,

**Table 1.** Demographical, clinical, and biochemical characteristics of the 2 groups.

| Variable | All (n=274) | Coronary artery ectasia group (n=137) | Control Group (n=137) | p |
|---|---|---|---|---|
| Age (years) | 59.1±9.3 | 60.5±10.8 | 57.5±7.3 | 0.007 |
| Gender (male, %) | 199 (72.6) | 100 (72.9) | 99 (72.3) | 0.892 |
| Body Mass Index, (kg/m$^2$) | 28.1±4.8 | 30.8±3.4 | 25.3±4.4 | <0.0001 |
| Hypertension, n (%) | 141 (51.5) | 80 (58.4) | 61 (44.5) | 0.022 |
| Diabetes Mellitus, n (%) | 144 (52.6) | 93 (67.9) | 51 (37.2) | <0.0001 |
| Heart Failure, n (%) | 15 (5.5) | 10 (7.3) | 5 (3.6) | <0.0001 |
| Coronary Artery Disease, n (%) | 112 (40.9) | 58 (42.3) | 54 (39.4) | 0.127 |
| Smoking, n (%) | 108 (39.4) | 69 (50.4) | 39 (28.5) | <0.0001 |
| Cerebrovascular Accident, n (%) | 8 (2.9) | 4 (2.9) | 4 (2.9) | 0.639 |
| Chronic Obstructive Pulmonary Disease, n (%) | 33 (12.0) | 20 (14.6) | 13 (9.5) | 0.194 |
| Chronic kidney disease, n (%) | 4 (1.5) | 2 (1.5) | 2 (1.5) | 0.748 |
| Atrial Fibrillation, n (%) | 12 (4.4) | 8 (5.8) | 4 (2.9) | 0.238 |
| History of Malignancy, n (%) | 7 (2.6) | 4 (2.9) | 3 (2.2) | 0.702 |
| Left ventricular ejection fraction, (%) | 52.1±10.1 | 49.4±11.5 | 51.2±10.6 | 0.056 |
| Laboratory Parameters | | | | |
| Creatinine (mg/dl) | 0.8±0.3 | 0.9±0.3 | 0.7±0.2 | 0.010 |
| Glomerular Filtration Rate, (ml/dk/1.73 m$^2$) | 88.9±17.5 | 88.1±19.9 | 93.8±13.1 | 0.041 |
| Fasting blood glucose, (mg/dl) | 100.5±12.9 | 107.4±12.1 | 93.7±9.6 | <0.0001 |
| Albumin, (g/dl) | 4.2±0.4 | 4.2±0.3 | 4.2±0.4 | 0.758 |
| Total Cholesterol, (mg/dl) | 200.9±45.4 | 221.1±41.1 | 180.8±40.4 | <0.0001 |
| Low Density Lipoprotein, (mg/dl) | 121.3±33.2 | 124.5±30.2 | 118.2±35.8 | 0.120 |
| High Density Lipoprotein Cholesterol, (mg/dl) | 43.3±11.4 | 36.1±6.7 | 50.5±10.6 | <0.0001 |
| Triglyceride, (mg/dl) | 157.6±71.9 | 210.3±58.9 | 104.9±36.4 | <0.0001 |
| Hemoglobin (g/dl) | 13.5±1.6 | 14.1±1.7 | 13.6±1.2 | 0.428 |
| Platelet, (10$^9$/L) | 247.7±61.3 | 251.3±62.7 | 244.1±59.8 | 0.329 |
| White blood cell, (10$^9$/L) | 8.6±5.7 | 9.5±7.8 | 8.6±1.9 | 0.057 |
| Neutrophil to lymphocyte ratio | 4.3±1.5 | 4.8±1.9 | 3.7±0.5 | <0.0001 |
| C-reactive Protein (mg/dL) | 3.9 (0.3-41.2) | 4.9 (3.2-41.2) | 3.9 (0.3-18.0) | 0.081 |
| Thyroid Stimulating Hormone (mU/L) | 2.3±1.6 | 2.3±1.9 | 2.3±1.1 | 0.917 |

**Table 2.** Univariate and multivariate forward stepwise logistic regression analysis: predictors of presence of coronary artery ectasia in patients presenting with acute coronary syndrome.

| | Univariate OR | 95% CI | p | Multivariate OR | 95% CI | p |
|---|---|---|---|---|---|---|
| Age | 1.036 | 1.009-1.064 | 0.008 | 1.458 | 1.098-1.936 | 0.009 |
| Body Mass Index | 1.398 | 1.288-1.517 | <0.0001 | 1.572 | 1.254-1.712 | <0.0001 |
| Diabetes mellitus | 1.564 | 1.135-1.868 | <0.0001 | 1.172 | 1.093-1.251 | <0.0001 |
| Hypertension | 0.572 | 0.354-0.923 | 0.022 | 0.120 | 0.004-0.344 | 0.015 |
| Heart Failure | 1.319 | 0.603-1.845 | 0.998 | | | |
| Smoking | 0.392 | 0.238-0.647 | <0.0001 | 0.282 | 0.018-0.437 | 0.008 |
| Creatinine | 1.263 | 0.892-1.347 | 0.053 | | | |
| Glomerular Filtration Rate | 1.066 | 0.951-1.381 | 0.127 | | | |
| Fasting blood glucose | 1.129 | 1.094-1.164 | <0.0001 | 1.341 | 1.066-1.686 | 0.012 |
| Total Cholesterol | 1.023 | 1.017-1.030 | <0.0001 | 0.971 | 0.929-1.016 | 0.202 |
| High Density Lipoprotein Cholesterol | 0.813 | 0.773-0.855 | <0.0001 | 0.699 | 0.556-0.880 | 0.002 |
| Triglyceride | 1.048 | 1.037-1.058 | <0.0001 | 1.154 | 1.044-1.276 | 0.005 |
| Neutrophil to lymphocyte ratio | 0.323 | 0.221-0.472 | <0.0001 | 0.421 | 0.110-0.608 | 0.001 |

and biochemical characteristics of the 2 groups are presented in detail in Table 1.

The variables (age, HT, DM, smoking, plasma total cholesterol, HDL, triglyceride, LDL, fasting blood glucose, and BMI) were analyzed if they have impact on Markis classification. There was no difference between 4 groups in terms of age, HT, smoking, plasma lipid profile and fasting blood glucose. While BMI was significantly different between Markis type-ll and Markis type-lll (p=0.002) and DM between Markis type-l and Markis type-ll (p=0.004), as well.

To further evaluate individual risk factors for CAE pres-

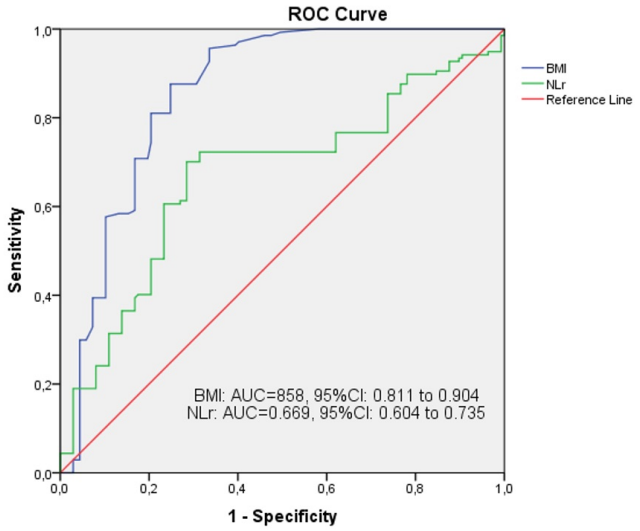


**Figure 1.** ROC curves of Body mass index and Neutrophil/Lymphocyte ratio in predicting presence of coronary artery ectasia in patients presenting with acute coronary syndrome.

ence, univariate logistic regression analysis was performed for age, BMI, DM, HT, history of HF, smoking status, serum creatinine, GFR, fasting blood glucose, total cholesterol, HDL, triglyceride, NLr, respectively. By univariate logistic regression analysis, age, BMI, DM, HT, smoking status, fasting blood glucose, total cholesterol, HDL, triglyceride and NLr were found to be correlated with CAE presence in ACS patients. These variables were included in the multivariate logistic regression model and age [p=0.009, $\beta$: 1.458, OR (95% CI): 1.098-1.936], DM [p<0.0001, $\beta$: 1.172, OR (95% CI): 1.093-1.251], HT [p=0.015, $\beta$: 0.120, OR (95% CI): 0.004-0.344], smoking status [p=0.008, $\beta$: 0.282, OR (95% CI): 0.018-0.437], fasting blood glucose [p<0.0001, $\beta$: 1.341, OR (95% CI): 1.066-1.686], HDL [p=0.002, $\beta$: 0.699, OR (95% CI): 0.556-0.880], triglyceride [p=0.005, $\beta$: 1.154, OR (95% CI): 1.044-1.276], NLr [p=0.001, $\beta$: 0.421, OR (95% CI): 0.110-0.608] and BMI [p<0.0001, $\beta$: 1.572, OR (95% CI): 1.254-1.712] were found as independent risk factors associated with CAE presence in patients presenting with ACS (Table 2). ROC curve analysis was performed to identify the optimal cut-off value and area under the curve (AUC) for BMI and NLr. ROC curve for accuracy of BMI and NLr for predicting CAE presence in patients presenting with ACS, is shown in Figure 1. The AUC for NLr was 0.669 [%95 CI: 0.604-0.735]. A cut off value of 4.8 for NLr was associated with 67.3% sensitivity and 66.2% specificity in prediction of CAE. Moreover, AUC for BMI was 0.858 [%95 CI: 0.811-0.904]. A cut off value of 27.4 for BMI was associated with 81.0% sensitivity and 80.4% specificity in prediction of CAE.

## Discussion

In this cohort, we sought to analyze the relation between being OW or obese and presence of CAE in patients presenting with ACS. Patients who were presented with ACS involving a CAE segment were in higher BMI tertials when compared to those without CAE. Higher prevalence of patients with CAE in the highest BMI values suggest metabolic deterioration in the symptomatic stage of the disease. Our results revealed a strong correlation between BMI and presence of CAE in patients presenting with ACS. A cut off value of 27.4 for BMI was associated with 81.0% sensitivity and 80.4% specificity in prediction of CAE.

Presence of CAE is known to be associated with thrombus formation and myocardial ischemia. Atherosclerotic risk factors and inflammation are defined underlying mechanisms for CAE presence. Elevated inflammatory markers such as matrix metalloproteinase, interleukin-6, C-reactive protein may promote ectasia development by weakening vessel wall. Smoking is thought to be responsible for inflammatory changes during atherosclerosis [28]. The higher prevalence of current smoking and NLr in CAE group emphasize the role of inflammation in our study. On the other hand, insulin resistance is known to accelerate atherosclerosis. Considering the linkage between obesity and metabolic syndrome, obese patients may be prone to ectasia development via insulin resistance pathway in addition to endothelial dysfunction, proinflammatory and thrombotic status [29]. Moreover, smoking, DM and HT were established as independent risk factors for presence of CAE in patients presenting with ACS. HT is a well-known risk factor either for atherosclerosis and CAE. Both HT and inflammation are assumed to facilitate the weakening of media layer of the coronary artery [30]. Higher fasting blood glucose, triglyceride and lower HDL levels are components of metabolic syndrome and those were found as independent risk factors related with presence of CAE in patients presenting with ACS. Aggressive management of modifiable risk factors and measures to deal with metabolic syndrome are utmost importance to prevent CAE development.

There is conflicting data regarding the association between obesity and cardiovascular risk. The relation between obesity (or being OW) and cardiovascular diseases was shown to be driven by accompanying DM, dyslipidemia and HT in previous studies [7], however, the high risk remained even after managing accompanying co-morbidities in another study [2]. Obese patients without concomitant metabolic syndrome were not found to have elevated risk for ACS [3,31]. Only individuals presenting with ACS were included in our study and DM, HT and hyperlipidemia were detected independent risk factors for CAE presence. However, waist circumference, as a component of metabolic syndrome, was not evaluated due to retrospective design of the study.

Coronary artery ectasia was most commonly observed in right coronary artery (RCA) and least frequently in the left main coronary artery (LMCA) according to literature [32-34], however CAE was most frequently observed in the RCA and followed by LAD, CX, and LMCA, respectively in our study. In the study of Markis et al., type I ectasia was the most common type , followed by type II, type III, and type IV [11]. There is conflicting reports about the frequency of the ectasia types; type III ectasia was reported as the most common, with other types occurring with similar frequency by a previous study [29], addition-

ally, type II ectasia was detected as the most and type I detected as the least common type in our current study.

*Limitations*

Single-center and retrospective design with a relatively small patient population were the main limitations of the study. CAE diagnosis was made visually, based on classical definition however using advanced imaging methods such as intravascular ultrasound may confirm diagnosis and give additional information about the vessel wall. It would be more reliable to define the inflammatory status by measuring more sensitive biomarkers rather than NLr. Definitely, larger and prospectively designed studies are needed to demonstrate the relationship between obesity and CAE especially in patients presenting with ACS and searching the role of weight loss as a disease modifier.

## Conclusion

In this study, obesity (being OW or obese) was found as an independent risk factor associated with the presence of CAE in patients presenting with ACS.

Furthermore, advanced age, current smoking, history of HT, DM and increased NLr are found to be linked with CAE presence in ACS patients. The higher triglyceride and fasting blood glucose and lower HDL levels support the idea that metabolic syndrome plays a role and insulin resistance is the underlying mechanism. Since coronary artery ectasia is linked with acute coronary syndrome and worse clinical outcomes, modifying risk factors and dealing with obesity is crucial.

*Ethics approval*

The study protocol was approved by the Bagcilar Training and Research Hospital KAEK in agreement with the Declaration of Helsinki (2022/11/08/029).

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