Increased Remnant Cholesterol Blood Concentration Associated with First Acute Coronary Syndrome

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ABSTRACT

Introduction: This study aimed to investigate the association between remnant cholesterol and acute coronary syndrome (ACS) and its predictive value for acute coronary syndrome occurring for the first time.

Patients and Methods: We compared increasing concentrations of non-fasting remnant cholesterol aside from other lipid profile parameters to investigate this association in 226 patients with ACS for the first time and 192 elective coronary angiography patients with normal coronary arteries.

Results: Patients with ACS were mostly males and were younger than those in the control group; moreover, they had higher percentage of diabetes mellitus (for all $p< 0.001$). Glucose and white blood cell levels at admission were also higher in patients with ACS. Remnant cholesterol level (such as LDL-C) was statistically higher in the ACS group compared with those of the control group ($p< 0.001$). In the univariate and bivariate binary logistic regression analysis, high blood remnant cholesterol, high blood LDL-C, and low blood HDL-C levels had a predictive value for ACSs.

Conclusion: This study demonstrated that remnant cholesterol levels (such as high blood LDL-C levels) are associated with increased risk of ACS for the first time. Further studies should be performed focusing on lowering remnant cholesterol levels apart from lowering LDL-C levels in patients with ACS.

Key Words: Acute coronary syndrome; remnant cholesterol; triglyceride-rich lipoproteins

Artmış Kalıntı Kolesterol Kan Düzeyleri İlk Defa Geçirilen Akut Koroner Sendrom ile İlişkilidir

ÖZET

Giriş: Açlık dışı kalıntı kolesterolün artması, artmış düşük dansiteli lipoprotein kolesterol (LDL-C) gibi iskemik kardiyovasküler hastalıklar için artmış risk ile ilişkilidir. Çalışmamızın amacı, ilk kez akut koroner sendrom (AKS) ile gelen hastalarda kalıntı kolesterol ve akut koroner sendromun arasındaki ilişkiyi araştırmaktır.

Hastalar ve Yöntem: İlk kez akut koroner sendrom ile başvuran 226 hasta ve normal koroner arter olarak sonuçlanmış 192 elektif koroner anjiyografi hastasında, diğer lipit profili parametrelerinin yanı sıra, açlık dışı kalıntı kolesterolün artan konsantrasyonlarını karşılaştırdık.

Bulgular: AKS hastaları kontrol grubu ile karşılaştırıldığında erkek cinsiyet fazla, daha genç ve daha fazla oranda diabetes mellitus mevcuttu (tümü için $p< 0.001$). AKS hastalarında glukoz ve beyaz kan hücresi düzeyleri de daha yüksekti. Kalıntı kolesterol, LDL-C değerine benzer şekilde, AKS grubunda istatistiksel olarak kontrol grubu ile karşılaştırıldığında daha yüksekti ($p< 0.001$). Tek değişkenli ve çok değişkenli ikili lojistik regresyon analizinde yüksek kan kalıntı kolesterolü, yüksek kan LDL-C değerleri ve düşük kan HDL-C değerleri ile akut koroner sendromlar arasında anlamlı bir ilişki mevcuttu.

Sonuç: Çalışmamız, yüksek kan LDL-C seviyelerinde olduğu gibi artmış kalıntı kolesterol düzeylerinin artmış ilk kez yaşanılan AKS riski ile ilişkili olduğunu göstermiştir. AKS hastalarında LDL-C düzeylerinin düşürülmesinin yanı sıra kalıntı kolesterol düzeylerinin düşürülmesi üzerine daha fazla çalışma yapılmalı ve odaklanılmalıdır.

Anahtar Kelimeler: Akut koroner sendrom; kalıntı kolesterol; trigliseritten zengin lipoproteinler

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INTRODUCTION

Dyslipidemia is one of the major cardiovascular risk factors. Patients with acute coronary syndrome (ACS) are treated with lipid-lowering treatment to control the low-density lipoprotein cholesterol (LDL-C) levels as secondary prevention in line with current dyslipidemia guidelines[1]. Cardiovascular risk remains after LDL-C goals are achieved with lipid-lowering treatments in these high-risk patients[2,3]. However, patients may still have residual dyslipidemia, which can be attributed partially to triglyceride-rich lipoproteins, especially remnant cholesterol[4-6].

Remnant cholesterol is the cholesterol content of triglyceride-rich lipoproteins and is composed of very low-density lipoproteins (VLDL) and intermediate-density lipoproteins (IDL) in the fasting state and of VLDL, IDL, and chylomicron in the non-fasting state. High concentrates of remnant cholesterol is causally associated with increased ischemic heart disease like high concentrates of LDL-C[7]. Additionally, non-fasting triglycerides were not only found to be associated with chronic ischemic heart disease, but they were also related with acute ischemic heart disease[8].

In the present study, we aimed to investigate whether remnant cholesterol is higher in patients with first ACS compared with that of the controls, and whether it has a predictive value, like LDL-C, on the development of ACS.

PATIENTS and METHODS

The study protocol was approved by institutional review boards and ethics committees and was conducted according to the Helsinki Declaration. Informed consent was obtained from all participants. All participants were white of Turkish descent.

Two hundred and twenty-six patients with ACS (firstly diagnosed with ST segment elevation myocardial infarction, non-ST segment elevation myocardial infarction, and unstable angina pectoris) who firstly had been hospitalized and underwent cardiac catheterization were enrolled in the study. One hundred and ninety two healthy individuals who were admitted to the cardiology department and who underwent elective cardiac catheterization resulting in normal coronary arteries were enrolled in the study as control group. Blood samples were drawn at admission in fasting state. Patients and control groups' remnant cholesterol as well as other lipids and lipoproteins were measured and calculated. Patients who had a previous history of cardiovascular disease, usage of lipid-lowering treatment, oral contraceptive therapy, hormone replacement therapy, severe or end-stage liver and kidney failure, heart failure, severe inflammation, or infective disease were excluded from the study.

Laboratory Analysis

Non-fasting total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) were measured by colorimetric assays (Boehringer Mannheim, Mannheim, Germany, Konelab, Thermo Fisher Scientific, Waltham, Massachusetts). LDL-C was calculated with the Friedewald equation when triglycerides were < 4 mmol/L (354 mg/dL); otherwise, it was measured directly[9]. Non-fasting remnant cholesterol was calculated as non-fasting total cholesterol minus HDL-C minus LDL-C.

Other Covariates

Hypertension was confirmed when systolic pressure was > 140 mmHg (135 mmHg for individuals with diabetes mellitus), when diastolic pressure was > 90 mmHg (> 85 mmHg for individuals with diabetes mellitus), and/or when there is usage of antihypertensive medication. Diabetes mellitus (DM) was confirmed when there is usage of antidiabetic medication and/or with a non-fasting glucose > 11 mmol/L (198 mg/dL) and/or hospitalization due to DM. A diagnosis of chronic obstructive pulmonary disease (COPD) is confirmed when a patient has symptoms of COPD (generally defined as a post-bronchodilator FEV_1-FVC ratio less than 0.70) in the absence of an alternative explanation for the symptoms.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median plus interquartile range, whereas categorical variables were expressed as count (n) and percent (%) values. Kolmogorov-Smirnov test was utilized to define the normality of data across two groups. Similarly, student-t test and Mann-Whitney U tests were used appropriately for comparisons. Pearson's chi-squared test was used for comparison of categorical variables. In addition, univariate and multivariate binary logistic regression analysis was performed to investigate independent correlates of ACS. Variables with a p value < 0.10 in univariate analysis were included in the multivariate regression analysis. All analysis was performed on statistical package software (SPSS ver. 22.0; SPSS Inc. Chicago, Illinois, USA), and p value < 0.05 was found to be statistically significant.

RESULTS

Table 1 shows the demographic properties and risk factors related to ACS and control group. The patients with ACS were younger compared with the control group (p< 0.001). Additionally, patients with ACS were mostly male and had more percentage of DM (for both p< 0.001). As it was shown in Table 2, glucose and white blood cell counts (WBC) were higher in the ACS group compared with the control group (p= 0.014 and p=

Table 1. Demographic properties and risk factors of acute coronary syndrome and control groups

Variables	Control group (n= 192)	ACS group (n= 226)	p
Age (years)	59.5 ± 11.1	54.8 ± 10.6	**< 0.001**
Male sex, n (%)	87 (45.3)	167 (73.9)	**< 0.001**
HT, n (%)	101 (52.6)	123 (54.4)	0.753
DM, n (%)	42 (21.9)	88 (38.9)	**< 0.001**
Smoking, n (%)	33 (17.2)	44 (19.5)	0.549
COPD, n (%)	14 (7.3)	10 (4.4)	0.657

ACS: Acute coronary syndrome, HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease.
Bold values indicate a p value < 0.05.

Table 2. Laboratory findings of acute coronary syndrome and control groups

Variables	Control group (n= 192)	ACS group (n= 226)	p
Glucose	121.1 ± 39.0	137.3 ± 38.9	**0.014**
Urea	36.3 ± 19.0	37.0 ± 11.8	0.663
Creatinine	1.3 ± 0.4	1.1 ± 0.2	0.311
WBC	8.3 ± 2.3	11.8 ± 3.2	**0.001**
Hemoglobin	13.2 ± 1.6	13.3 ± 1.7	0.686
Platelet	247.9 ± 63.2	238.5 ± 70.1	0.156
Total cholesterol	193.1 ± 35.2	204.4 ± 33.1	**0.001**
LDL-C	118.1 ± 24.9	126.6 ± 27.8	**0.001**
HDL-C	45.9 ± 10.2	36.4 ± 8.5	**< 0.001**
Triglyceride	119 (88.3-167.5)	179 (129.8-209.3)	**< 0.001**
Remnant cholesterol	24 (18-34)	37 (26.8-51)	**< 0.001**

ACS: Acute coronary syndrome, WBC: White blood cell, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol.
Bold values indicate a p value < 0.05.

0.001, respectively). Remnant cholesterol was also statistically higher in the ACS group compared with the control group like other cholesterol levels (p< 0.001).

Table 3 demonstrates the univariate and multivariate binary logistic regression analysis of lipid parameters. High blood remnant cholesterol had a predictive value on ACSs as well as high blood LDL-C values and low blood HDL-C levels. Total cholesterol and triglyceride did not have an association on predicting ACSs as stated in our analysis. Additionally, age, sex, and WBC values had a predictive value on ACSs.

DISCUSSION

It was found in the present study that patients with ACS had worse values of lipid parameters compared with patients with normal coronary artery. Glucose, in parallel with DM frequency, and WBC were also higher in patients with ACS. Additionally, high blood remnant cholesterol was associated with ACS and had a predictive value on ACS as well as LDL-C and low HDL-C. On the contrary, total cholesterol and triglyceride did not have any predictive value on acute cardiovascular events as demonstrated in our analysis.

In our study, remnant cholesterol was determined in the non-fasting state. By using non-fasting state, remnant cholesterol was calculated as non-fasting total cholesterol minus HDL-C minus LDL-C; therefore, remnant cholesterol can be calculated directly from a standard lipid profile. Thus, the presently used calculated remnant cholesterol comes at no extra cost and is easily available.

Increased blood levels of remnant cholesterol are thought to be causally related with atherosclerosis just as increased LDL-C does[10,11]. Remnant cholesterol including chylomicron remnants, VLDL, and IDL penetrate the arterial wall and appear to be selectively retained within the arterial intima[12-14], leading

Table 3. Univariate and multivariate binary logistic regression analysis of lipid parameters as a risk factor for prediction of acute coronary syndrome

Variables	Univariate OR and 95% CI	p	Multivariate OR and 95% CI	p
Age	1.04 (1.022-1.060)	< 0.001	**1.09 (1.060-1.134)**	**< 0.001**
Sex	3.41 (2.265-5.152)	< 0.001	**4.46 (2.162-9.219)**	**< 0.001**
DM	0.44 (0.286-0.683)	< 0.001	0.52 (0.247-1.080)	0.079
Total cholesterol	1.01 (1.004-1.016)	0.001	0.89 (0.865-0.918)	0.065
LDL-C	1.01 (1.005-1.020)	0.001	**1.11 (1.106-1.182)**	**< 0.001**
HDL-C	0.90 (0.871-0.919)	< 0.001	**0.85 (0.814-0.901)**	**< 0.001**
Triglyceride	1.01 (1.003-1.009)	< 0.001	0.99 (0.995-1.002)	0.376
Remnant cholesterol	1.04 (1.026-1.054)	< 0.001	**1.16 (1.117-1.196)**	**< 0.001**
Glucose	1.01 (1.001-1.009)	0.018	1.01 (0.997-1.010)	0.274
WBC	1.37 (1.261-1.489)	< 0.001	**1.26 (1.130-1.407)**	**< 0.001**

OR: Odds ratio, CI: Confidence interval, DM: Diabetes mellitus, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, WBC: White blood cell.
Bold values indicate a p value < 0.05.

to the accumulation of cholesterol, formation of foam cell, and development of atherosclerotic plaque[15]. In addition, remnant lipoproteins may increase the expression of inflammatory proteins, adhesion molecules, and coagulation factors, promoting the formation of foam cells[16]. Taken together, these data therefore make it reasonable that increased blood concentrations of remnant cholesterol in patients with ischemic heart disease could explain part of residual risk with respect to increased mortality as it was shown previously[17]. Our study supports that remnant cholesterol is associated with the growth of the coronary syndromes and may be considered to be one of the risk factors.

As it was specified by current European Society of Cardiology and ACC/AHA (The American College of Cardiology/American Heart Association) guidelines, LDL-C is the major component of target therapy in reducing cardiovascular risk and mortality[1,18]. Physicians are focused on treating patients with dyslipidemia and high risk of cardiovascular disease with statin treatment, mainly targeting LDL-C concentrations rather than on reducing triglycerides and remnant cholesterol[10]. Increased triglycerides have primarily been treated to prevent acute pancreatitis, and there still is no consensus whether to treat increased triglycerides to prevent cardiovascular disease, although such treatment is now recommended in some guidelines[19,20]. Our study provides further support for the usage of non-fasting triglycerides or remnant cholesterol as a potential target for treatment, particularly in patients with ACS.

It is compatible with the latest information that patients presenting with ACS in our study are mostly younger and are likely to be male participants. Another point is that higher levels of WBC in our study in patients with ACS support the atherosclerotic inflammatory component, which was demonstrated in previous studies investigating remnant cholesterol[21].

The present study has some limitations. Because there may be racial and genetic differences in the blood lipid profile in different countries or regions, our results may not necessarily apply to other racial groups. Another one is that we used only the first and single lipid blood profile of remnant cholesterol and LDL-C presuming that concentrations were constant over time. The use of single measurement of patients' lipid profile at study enrollment without repeated sampling may lead to regression dilution bias, given the variability of remnant cholesterol and LDL-C concentrations. However, in our study, we included the first non-fasting lipid values to show the difference in lipid profile between groups, and we used the values before the statin treatment for patients with ACS.

CONCLUSION

Our analysis demonstrated that remnant cholesterol levels, not total cholesterol levels, are associated with increased risk of first ACSs like high LDL-C levels. Further studies should be focused not only on lowering LDL-C concentrations but also on lowering remnant cholesterol. Physicians need to do more studies on this topic to get remnant cholesterol to be among the target treatments in current cardiology guidelines.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: NÖ, CK

Analysis/Interpretation: RA, OT

Data Acquisition: ZB, EE

Writting: CD

Critical Revision: OT

Final Approval: All of authors.

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