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Lower LDL-cholesterol levels associated with increased inflammatory burden in patients with acute ST-segment elevation myocardial infarction

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SUMMARY

OBJECTIVE: Association of low-density lipoprotein cholesterol and highly sensitive C-reactive protein in ST-elevation myocardial infarction patients was assessed in this study.

METHODS: 591 consecutive patients who were hospitalized with a diagnosis of ST-elevation myocardial infarction were enrolled and assigned into tertiles according to their serum low-density lipoprotein cholesterol levels. Differences in highly sensitive C-reactive protein among low-density lipoprotein cholesterol tertiles and correlations between highly sensitive C-reactive protein and low-density lipoprotein cholesterol were assessed.

RESULTS: Highly sensitive C-reactive protein levels differed significantly among the groups (p<0.001) and found to be highest in the low-density lipoprotein cholesterol tertile 1 and lowest in the low-density lipoprotein cholesterol tertile 3 (post-hoc p-values: tertile 1 vs. 2 <0.001; tertile 1 vs. 3 <0.001; tertile 2 vs. 3=0.019). There was a negative correlation between hs-CRP and both low-density lipoprotein cholesterol (r=-0.332, p<0.001) and total cholesterol (r=-0.326, p<0.001). There was also a negative correlation between highly sensitive C-reactive protein and high-density lipoprotein cholesterol, though the strength of this relationship was weak (r=-0.103, p=0.014).

CONCLUSION: Lower low-density lipoprotein cholesterol levels are associated with higher inflammatory burden in patients with acute STEMI. Further studies are required to elucidate the significance of low-density lipoprotein cholesterol levels in ST-elevation myocardial infarction settings.

KEYWORDS: ST elevation myocardial infarction. Cholesterol, LDL. Hs-CRP.

INTRODUCTION

Elevated low-density lipoprotein cholesterol (LDL) is one of the most emphasized risk factors for cardiovascular disease (CVD). Results of the studies evaluating the effect of statins on LDL reduction led up to the motto "the lower the better" for prevention of CVD[1,2]. Inversely, lower LDL levels were noticed in acute myocardial infarction (AMI) patients for more than 50 years[3,4]. Subsequent studies revealed that serum cholesterol levels fall rapidly after an AMI such that serum LDL decreased 48% below baseline on the 7th day of AMI[5-8]. Moreover, several studies showed worse clinical outcomes in AMI and heart failure patients with lower total cholesterol (TC) and LDL levels indicated a "cholesterol paradox"[9-14]. Previously, several clinical studies demonstrated

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the acute phase reactant properties of serum lipoproteins in bacterial and viral infections in humans[15,16]. Alterations in LDL levels in heart failure and its prognostic impact were also largely explained by acute phase reactant properties of serum lipoproteins[10]. Thus, LDL levels may have the potential to be an inflammatory marker in AMI. However, association of LDL and inflammatory burden in AMI patients were not assessed before. Thus, the relationship of serum LDL with highly sensitive C-reactive protein (hs-CRP) in patients with ST-segment elevation myocardial infarction (STEMI) was investigated.

METHODS

We retrospectively enrolled 591 consecutive patients who were hospitalized with a diagnosis of STEMI. Patients were enrolled into the study if their hs-CRP levels and fasting lipid profiles were available within 24 hours after the onset of symptoms. Medical history of the patients were obtained from medical records. Forty six patients were excluded from the study due to the use of lipid-lowering medications. In order to perform analysis, the patients were assigned into tertiles according to their serum LDL levels. STEMI was defined as ≥1 mm ST-segment elevation in at least two contiguous electrocardiogram leads, except V2-V3, which required 1.5 mm for female patients, 2 mm for male patients >40 years of age, and 2.5 mm for male patients <40 years old or new onset left bundle-branch block in the presence of ischemia symptoms. A transthoracic echocardiography was performed 48 to 72 hours after admission using a Vivid 7 system (GE Medical Systems, Milwaukee, WI, USA) and the left ventricular ejection fraction was calculated by the modified Simpson method. Serum levels of hs-CRP were measured using the latex enhanced immune-turbidimetric method (Cardio-Phase High Sensitivity C-Reactive Protein; Siemens Healthcare Diagnostics Inc., Tarrytown, New York, USA). Serum TC, triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) concentrations were analyzed by a BM-Hitachi-747 auto-analyzer (Boehringer Mannheim GmbH, Mannheim, Germany). Serum LDL-C values were estimated by the formula of Friedewald et al. or directly measured if TG>400 mg/dL[17]. The study protocol was approved by the Local Ethics Committee.

SPSS Statistics, version 17.0 (SPSS Inc, Chicago, IL), was used for statistical analysis. Kolmogorov-Smirnov test was used to determine the distribution patterns. Data were presented as mean and standard deviation, median and interquartile range, or proportions as appropriate. The one-way ANOVA was used to compare data with normal distribution and Kruskal-Wallis test was used to compare the data without normal distribution. Bonferroni correction was used for multiple comparisons. Pearson's correlation analysis was used to assess the correlation between hs-CRP and serum lipid parameters. Categorical variables were compared with the χ^2 test. A two-tailed p-value<0.05 was considered to be statistically significant.

RESULTS

Every LDL tertile contains 197 patients. Mean age of the participants was 61.71. There was no difference in regard to demographic characteristics among the LDL tertiles. Time to lipid measurement was also similar. Mean LDL level was 75.59±17.207 for tertile 1, 115.79±9.487 for tertile 2, and 161.61±25.968 for tertile 3 (Table 1). hs-CRP levels differed significantly among the groups (p<0.001) and found to be highest in tertile 1 and lowest in tertile 3 (post-hoc p-values: tertile 1 *vs.* 2 <0.001; tertile 1 *vs.* 3 <0.001; tertile 2 *vs.* 3 =0.019). Mean troponin T level was 25.3±14.7 in tertile 1, 19.5±15.5 in tertile 2, and 16.6±12.2 in tertile 3 (p=0.01). There was a negative correlation between hs-CRP and both LDL (r=-0.332, p<0.001) and TC (r=-0.326, p<0.001). There was also a negative correlation between hs-CRP and HDL, though the strength of this relationship was weaker (r=-0.103, p=0.014). There was no correlation between hs-CRP and TG. (Figure 1)

DISCUSSION

In the present study, the association of serum LDL with hs-CRP in STEMI patients was association and it was found that hs-CRP levels are higher in the lowest LDL tertile and lower in the highest LDL tertile. In addition, there was a negative correlation between LDL and hs-CRP in this patient group. Moreover, hs-CRP was negatively correlated with both TC and HDL. Troponin T levels were also higher in the lowest LDL tertile and lower in the highest LDL tertile. To the best of our knowledge, this the first study in the literature revealing the inverse association of hs-CRP with serum LDL in STEMI patients.

Previous studies showed that marked changes in serum lipoproteins occur during the course of AMI including reductions in TC, LDL, and HDL and increases in TG[4-8]. Infarction size is probably important in reducing LDL, as shown in the study of Rott et al., which suggested that LDL levels decrease significantly after an AMI and the reduction is correlated with cardiac troponin T levels[18]. Several mechanisms were proposed to explain the lipoprotein alterations after AMI. First, it was shown that acute phase response causes up-regulation of LDL receptor

Table 1. Demographic, clinical, and laboratory characteristics of study participants.

	Tertile 1, n=197	Tertile 2, n=197	Tertile 3, n=197	p-value
Age (years)	62.93±11.62	61.79±13.05	60.43±11.39	0.09
Male gender – n (%)	154 (78.2)	136 (69.90)	133 (67.5)	0.055
Body mass index (kg/m^2)	28.0±4.6	28.0±4.3	28.0±4.4	0.319
Hypertension – n (%)	80 (40.6)	88 (44.7)	83 (42.1)	0.712
Diabetes – n (%)	77 (39.1)	62 (31.5)	62 (31.5)	0.183
Smoking – n (%)	71 (36.0)	93 (47.2)	100 (50.8)	0.009
Prior MI – n (%)	19 (9.6)	8 (4.1)	14 (7.1)	0.092
Prior stroke – n (%)	8 (4.1)	5 (2.5)	6 (3.0)	0.600
Glucose (mg/dL)	160.5±83.9	153.6±81.5	143.6±72.5	0.107
Creatinine (mg/dL)	1.12±26	1.09±25	1.03±21	0.001
CK-MB (mg/dL)	75.14±39.76	77.88±39.41	76.71±39.11	0.955
Troponin T	25.3±14.7	19.5±15.5	16.6±12.2	0.010
Cholesterol (mg/dL)	143.0±23.6	187.8±17.8	241.8±41.9	<0.001
LDL-C (mg/dL)	75.59±17.2	115.79±9.5	161.61±25.9	<0.001
HDL-C (mg/dL)	38.33±9.922	41.45±9.312	42.84±9.613	<0.001
Triglyceride (mg/dL)	142.1±78.3	152.6±76.6	185.7±110.4	<0.001
Hs-CRP (mg/L)	7.19±3.38	5.93±2.98	5.09±2.76	<0.001
Hemoglobin (g/dL)	14.16±1.53	14.43±1.46	14.54±1.44	0.061
WBC (x10,000/mL)	10.89±3.50	10.85±3.42	10.59±3.33	0.639
Platelets (x1,000/mL)	222.29±65.48	240.46±62.38	243.05±59.47	0.002
LVEF (%)	46.20±11.78	48.44±9.44	48.26±9.93	0.080
Pulse rate (min^{-1})	79.93±15.54	79.89±14.83	79.16±13.56	0.842
Systolic BP (mmHg)	124.97±22.01	131.39±24.03	132.32±26.94	0.005
Diastolic BP (mmHg)	76.43±13.073	79.17±13.425	79.71±15.062	0.044
Syntax Score	16.69±10.51	15.36±9.25	15.08±9.01	0.210
Time to lipid measurement (h)	6 (4-8)	7 (4-8)	6 (4-8)	0.374
Initial Treatment				
Medical-Fibrinolytic	6 (3.0)	4 (2.0)	9 (4.5)	0.356
PCI-stent	162 (82.2)	172 (87.3)	168 (85.3)	
CABG	29 (14.8)	21 (10.7)	20 (10.2)	

MI: myocardial infarction; CK-MB: creatinine kinase myocardial band; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; hs-CRP: high sensitivity C-reactive protein; WBC: white blood cell; LVEF: left ventricular ejection fraction; BP: blood pressure; PCI: percutaneous coronary intervention; CABG: coronary artery by-pass graft operation.

activity and reduction in some HDL regulatory proteins[19,20]. In addition, myocardial necrosis facilitates adrenergic-mediated adipocyte lipolysis leading to free fatty acid mobilization, increased hepatic very low density lipoprotein (VLDL) secretion, TG elevation, and alteration in LDL and HDL particle composition[21,22]. Other possible contributors to lipid changes after AMI include in-hospital therapy and lifestyle changes such as heparin, which causes lipoprotein lipase-mediated TG hydrolysis, beta-blockers which suppress hormone-sensitive lipase, postural effects and reduction of saturated fat intake[23-28].

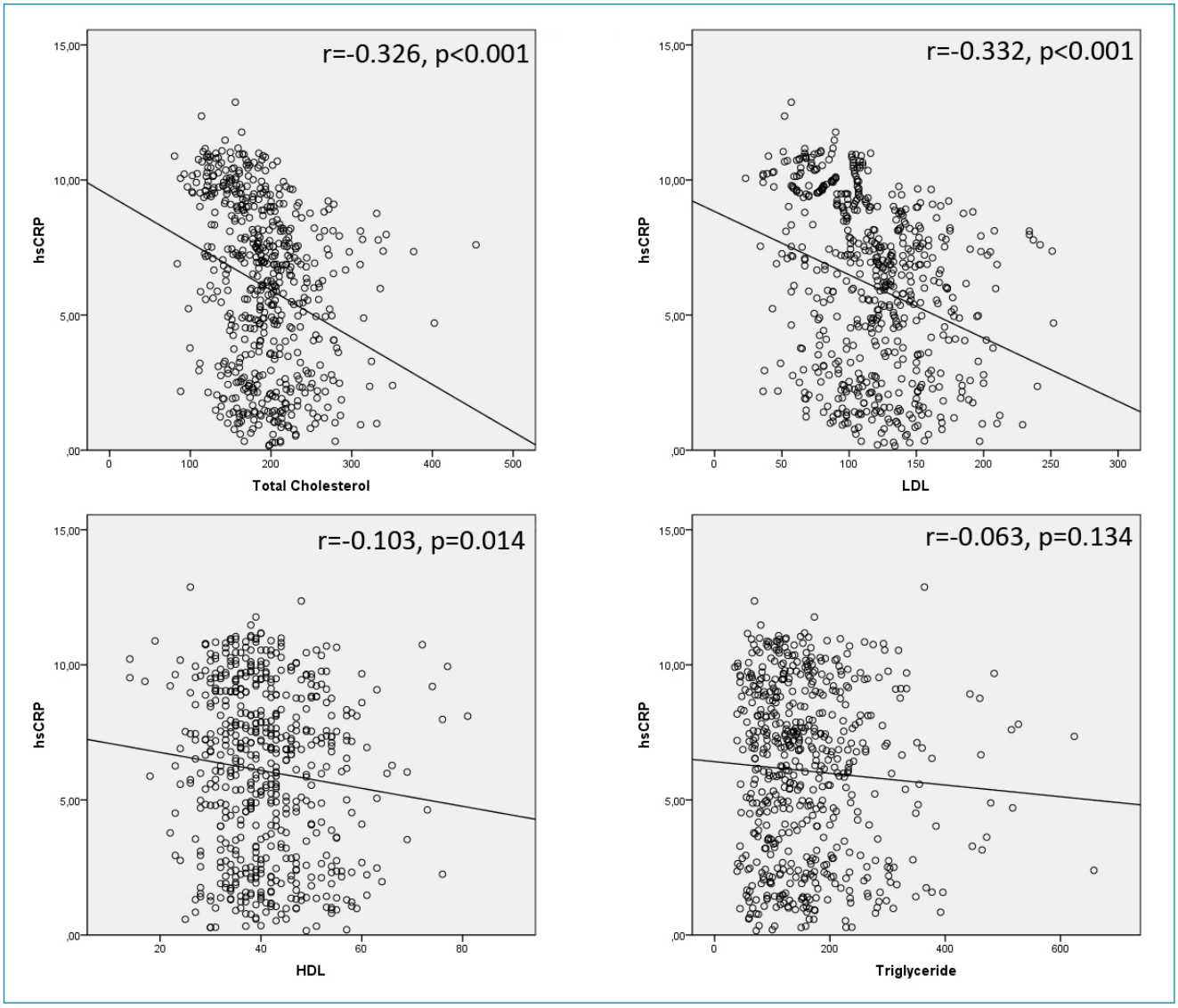

Figure 1. Scatterplots summarizing the correlations between hs-CRP and serum lipoproteins.

Impact of the low cholesterol levels on the prognosis of patients with CVD was investigated in some studies previously. In one of them, Richartz et al. found out that lower cholesterol levels were associated with poor survival in patients with advanced heart failure on mechanical support[9]. In another, Rauchhaus et al. demonstrated that lower cholesterol levels are associated with poor clinical outcome in patients with chronic heart failure regardless of the heart failure etiology. In addition, negative correlation of serum cholesterol and tumor necrosis factor alpha was revealed in this study[10]. A similar result was found in the study by Norwich et al., which showed that low serum TC, LDL, HDL, and TG are related to increased mortality in advanced heart failure[11]. In two studies about low LDL levels in myocardial infarction, Al-Mallah et al. found out that low LDL levels are associated with increased 3-year mortality in non STEMI and Reddy at al. demonstrated that low LDL levels are associated with higher in-hospital mortality after AMI[12-14].

Results of the present study revealing the relationship of hs-CRP and lipoprotein levels, support the hypothesis that AMI patients with lower LDL have higher inflammatory burden and acute phase response is responsible for lipoprotein changes after AMI. Cho et al. demonstrated that life-saving medications, including lipid-lowering drugs, were underused in MI patients with lower admission LDL levels[13]. Considering these patients have higher hs-CRP levels, hesitation to initiate adequate doses of lipid-lowering therapy due to low LDL levels may contribute to a worse prognosis.

The present study has several limitations that should be taken into account when interpreting its results. First, it is a retrospective and single center study. However, all consecutive cases in a period of time were enrolled in order to eliminate selection bias. In addition, preadmission serum lipoprotein levels of the patients were not available and serial measurements of LDL were not performed. Thus, exact changes in serum lipoproteins due to AMI were not available.

CONCLUSIONS

Results of the present study suggest that acute STEMI patients with lower LDL levels have higher inflammatory burden reflected by higher hs-CRP levels. Further prospective studies are needed to confirm this hypothesis and elucidate the clinical significance of the findings of this study.

AUTHORS' CONTRIBUTIONS

EA: Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **SKA:** Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **BY:** Conceptualization, Data Curation, Writing – Original Draft, Writing – Review & Editing. **AK:** Conceptualization, Formal Analysis, Writing – Original Draft, Writing – Review & Editing.

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