Relationship between Discordance of Low-Density Lipoprotein and Non-High-Density Lipoprotein Cholesterol and Risk Stratification in Acute Myocardial Infarction

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Abstract

Background: Sizeable proportion of patients have discordant low-density lipoprotein cholesterol (LDL-C) and non-high density lipoprotein cholesterol (NHDL-C). It has been shown that discordance of LDL-C and NHDL-C either underestimates or overestimates coronary risk.

Objective: We assessed whether this discordance has an impact on GRACE and TIMI risk scores in patients with acute myocardial infarction (AMI).

Methods: We retrospectively evaluated the data of 198 consecutive patients with AMI. Fasting serum lipid profiles were recorded, GRACE and TIMI scores were calculated. Patients were divided into 3 groups according to LDL-C and NHDL-C percentiles: Discordant group: LDL-C<NHDL-C (n=38), concordant group: LDL-C=NHDL-C (n=112) and discordant group LDL-C>NHDL-C (n=48). GRACE and TIMI scores, mortality and cardiovascular events (heart failure, non-fatal myocardial infarction and angina) at sixth month were compared between these three groups. Differences between these groups were analyzed with One-way ANOVA or Kruskal-Wallis rank test, and with chi-square for percentages. Also, post hoc LSD or Conover-Iman's non-parametric multiple comparison test were used. A p value <0.05 was accepted as statistically significant.

Results: TIMI risk score didn't differ between discordant or concordant groups. Mean GRACE (death) and GRACE (death and MI) scores were higher in group with LDL-C<NHDL-C than with LDL-C=NHDL-C and LDL-C>NHDL-C (p=0.029 and 0.008, respectively). Cardiovascular events and mortality at sixth month were not different among groups (p=0.473 and p=0.176, respectively).

Conclusion: GRACE score was higher in discordant group with LDL-C<NHDL-C, but there is no difference regarding TIMI scores between discordant and concordant groups in AMI patients.

Keywords: Atherosclerosis; Low Density Lipoprotein Receptor –Related Protein; Cholesteroç-HDL; Triglycerides; Cardiovascular Diseases/complications.

Introduction

Low-density lipoprotein-cholesterol (LDL-C) is the primary target of lipid lowering therapy to prevent atherosclerotic events.[1] However, despite the LDL-lowering therapy, some acute myocardial infarction (AMI) patients continue to have residual risk.[2]

Non-high-density lipoprotein-cholesterol (NHDL-C) is recommended as a secondary target for lipid management.[1] There is a growing body of evidence that NHDL-C is a better predictor of major cardiovascular events after AMI.[3] However, not all patients have concordant LDL-C and NHDL-C levels. It has been shown that discordance of LDL-C and NHDL-C either underestimates or overestimates coronary risk.[4]

The GRACE and TIMI risk scores are widely used models to assess patients prognosis after acute coronary

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syndromes.[5,6] They incorporate patient's characteristics, clinical and laboratory findings for risk stratification. In this study, we aimed to evaluate the relationship between discordance of LDL-C and NHDL-C and risk scores to find out whether the discordance of lipid parameters have impact on mortality after AMI.

Methods

This study assessed the data of 209 consecutive patients admitted to cardiology department with a diagnosis of acute myocardial infarction between January 2009 and June 2009. Among these, 11 patients were excluded because of incomplete data. Finally, we evaluated the data of 198 patients in our analysis. Exclusion criteria were as follows: age above 85 years old, clinical active infection, active malignancy, hematological or autoimmune disorders, receiving chemotherapy or steroids, cardiogenic shock, decompensated heart failure, arrhythmia with hemodynamic instability, and percutaneous coronary intervention or surgery within 30 days before admission. The assessed clinical parameters were age, gender and coronary risk factors. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or current medication with antihypertensive drugs. Patients were defined as diabetic if they had been informed of this diagnosis before and had been using oral antidiabetic drugs or insulin treatment on admission. Body mass index was calculated as body weight in kilograms divided by the squared value of body height in meters (kg/m²).

Type of acute coronary syndrome, admission blood pressure and heart rate, ST- segment changes in ECG, Killip classification or presence of cardiac arrest at admission, and ejection fraction were evaluated. GRACE and TIMI scores were calculated from the clinical history, electrocardiogram, and laboratory values collected on admission. TIMI risk score represents the sum of seven variables including age, >65 years, >3 risk factors for coronary artery disease, use of aspirin in the past 7 days, known coronary artery stenosis >50%, ≥ 2 episodes of angina within 24 hours, ST-segment deviation and elevated cardiac markers. One point is given to each of the variables present at the time of assessment. Higher risk score is correlated with increased incidence of death, myocardial infarction and revascularization. Grace score was calculated using GRACE 2.0 calculator at the time of admission by using the following variables: age, heart rate, systolic blood pressure, creatinine, cardiac arrest at admission, ST-segment deviation, elevated cardiac markers and Killip class. GRACE (death) represents in-hospital and 6-month mortality after a myocardial infarction and GRACE (death and MI) represents death or myocardial infarction from admission to six months after discharge. Also, in-hospital mortality and cardiovascular events at sixth month including angina, non-fatal myocardial infarction and heart failure were recorded. Data were obtained from patient files and hospital computer registry system. Also, 6-month mortality was assessed by contacting patients and their family with a telephone call.

The study was approved by the local Ethics Committee. Data from subjects were analyzed retrospectively.

Laboratory Measurements

Lipid measurements were performed on fasting blood samples that were taken before the angiography. Plasma concentrations of total cholesterol, LDL-C, HDL-C and triglyceride (TG) were measured with biochemistry analyzer (Abbott Architect c8000). The enzymatic colorimetric method was used for the quantitative determination of total cholesterol. Endpoint colorimetric method was used for the quantitative determination of HDL-C. Glycerol phosphate oxidase method was used for the quantitative determination of triglyceride. The Friedewald equation was used to calculate LDL-C.[7] NHDL-C was calculated as total cholesterol minus HDL-C.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) for normal distributions and median (interquartile range) for skewed distributions. Categorical variables were defined as numbers and percentages. Whether the distribution of continuous variables was normal or not was determined by Kolmogorov-Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Correlation between continuous variables including LDL-C and NHDL-C was examined with Spearman correlation analysis. Percentile distributions of LDL-C and NHDL-C were calculated. Discordance was determined based on the difference in the percentile of NHDL-C and percentile of LDL-C. Six percentile points was used as a cutoff so that the numbers of patients that would be classified as concordant or discordant were as close as possible. Patients were divided into 3 groups according to percentiles: Discordant group: LDL-C<NHDL-C

(n=38), concordant group: LDL-C=NHDL-C (n=112) and discordant group LDL-C>NHDL-C (n=48). Differences between baseline characteristics of patients across these groups were analyzed with One-way ANOVA for normally distributed variables, with Kruskal-Wallis rank test for not normally distributed variables, and with chi-square for percentages. When the p-value from One-Way ANOVA or Kruskal Wallis test statistics were statistically significant, post hoc LSD or Conover-Iman's non-parametric multiple comparison test were used to know which group differ from which others. A p value <0.05 was accepted as statistically significant. Data analyses were performed by using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States).

Results

The mean age of study population was 62.7±10.7 years and of the 198 patients 73.7% were males. More than half of the patients had hypertension, 30% had diabetes mellitus, 61% had any smoking history and 38% had dyslipidemia. Baseline characteristics are presented in Table 1. Fifty-one and a half percent of the patients had NSTEMI and 48.5% had STEMI. Mean difference between NHDL-C and LDL was 31.9±20.5 mg/dl. LDL-C levels were strongly and positively correlated with NHDL-C levels (r=0.858, p<0.001). In-hospital mortality rate was 2%. In 10 patients, death occurred during six months follow-up.

To further evaluate the characteristics of patients with discordance and concordance of LDL-C and NHDL-C, we classified patients into 3 subgroups according to percentiles: Discordant group: LDL-C<NHDL-C (n=38), concordant group: LDL-C=NHDL-C (n=112) and discordant group LDL-C>NHDL-C (n=48) (Figure 1). Gender, age, smoking history, percentage of patients with hypertension or percentage of patients with dyslipidemia were not different among the groups. Patients in the discordant group LDL-C<NHDL-C, had the highest prevalence of diabetes mellitus (p=0.013). Median TIMI score was not different among groups. Mean GRACE (death) score and GRACE (death and MI) score were highest in the discordant group LDL-C<NHDL-C than in the concordant group LDL-C=NHDL-C and the discordant group LDL-C>NHDL-C (p=0.029 and p=0.008, respectively) (Table 2). Cardiovascular events and mortality at sixth month were not different among groups (p=0.473 and p=0.176, respectively). Because of the small number of in-hospital deaths in each group, analysis of these subgroups regarding in-hospital mortality was not possible.

Discussion

In the present study, we assessed the cross-sectional association between LDL-C and NHDL-C discordance and Grace and TIMI scores. Median TIMI score was not different between discordant and concordant groups. Mean GRACE score was highest in the discordant group with LDL- C<NHDL-C.

Table 1 – Baseline characteristics of study population	
Characteristics	
Clinical characteristics	
Gender (% male)	73.7
Age (years) (mean±standart deviation)	62.7±10.7
Smoking (%)	61.6
Hypertension (%)	60.6
Diabetes (%)	30.3
Dyslipidemia (%)	37.9
Body mass index (kg/m²) (mean±standart deviation)	26.8±4.1
Biochemical analysis (mean±standart deviation)	
Total cholesterol (mg/dl)	185.8±41.4
LDL-C (mg/dl)	116.7±33.3
HDL-C (mg/dl)	37.1±9.8
Triglyceride (mg/dl)	162.7±112.9
NHDL-C (mg/dl)	148.6±40.1
Fasting glucose (mg/dl) glucose(mg/dl)	116.6±42.1
Creatinine (mg/dl)	1.1±0.55
Risk scores (mean±standart deviation)	
Mean GRACE (death) score	110.2±29.2
Mean GRACE (death and MI) score	124.3±44.0
Median TIMI score (interquartile range)	3.0(2.0)

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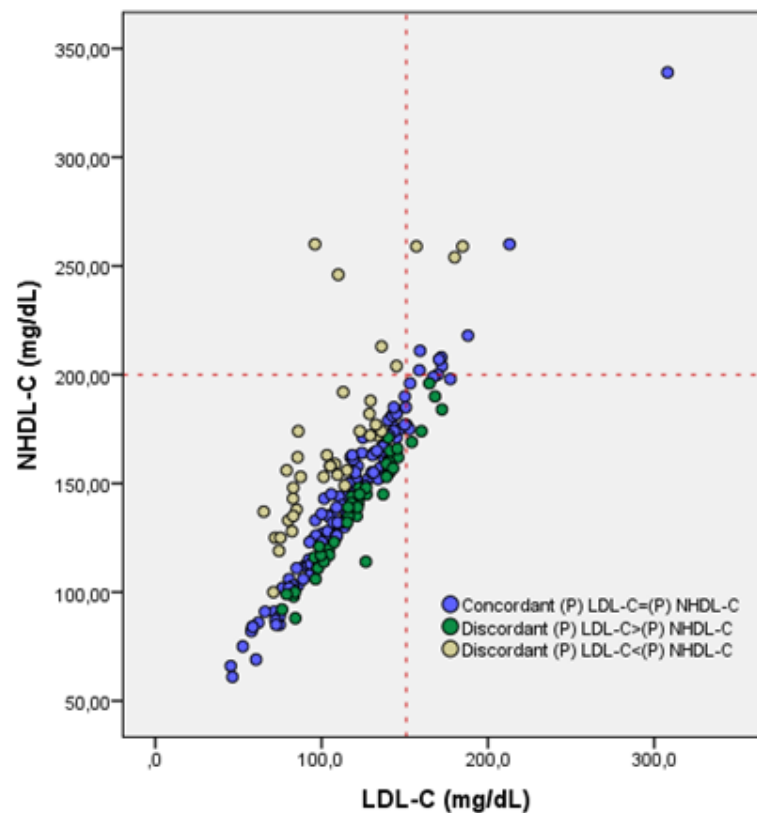Int J Cardiovasc Sci. 2021; 34(5):550-556
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Figure 1 – Scatterplots and prevalence of discordance and concordance defined according to percentiles of LDL-C and NHDL-C.

It has been demonstrated that NHDL-C is a predictor of cardiovascular disease mortality in individuals free of cardiovascular disease.[8-10] Also, it is associated with mortality in patients with coronary heart disease.[11] However, the studies specifically evaluated its role on cardiovascular mortality after an index myocardial infarction were limited. In one study, it has been reported that NHDL-C >130 mg/dl during follow-up after a myocardial infarction was associated with higher risk of long-term major cardiovascular events (MACE).[3] Besides all-cause death, myocardial infarction, stroke and cardiovascular hospitalization were other components of MACE in that study.

LDL-C is the main target for lipid lowering therapy after myocardial infarction in daily clinical practice.[1] In a recent study, LDL-C was found to be independently associated with increased cardiovascular disease mortality in individuals free of cardiovascular disease in 27-year follow-up period.[12] It has also been demonstrated that LDL-C levels predict coronary heart disease mortality in men with preexisting cardiovascular disease.[13,14]

However, studies evaluating LDL-C on prognosis after myocardial infarction have mixed results. In 2476 patients hospitalized for MI, small dense LDL was associated with low cardiovascular mortality.[15] In a study by Reddy et al. the lowest LDL-C levels were associated with highest risk of in-hospital mortality after myocardial infarction.[16]

Sizeable proportion of patients have discordant LDL-C and NHDL-C (high LDL-C and low NHDL-C, and vice versa). Discordance rate changes from 11% to 29% in previous studies.[4,17,18] It has been shown that discordance of LDL-C and NHDL-C either underestimates or overestimates coronary risk defined as non-fatal MI, percutaneous coronary intervention, coronary artery bypass grafting or coronary death.[4] It was suggested that the LDL-C alone may give a false sense of security with one fifth of the subjects still having high cardiovascular risk, despite having normal LDL-C levels.[19] Studies evaluating the impact of discordance of LDL-C and NHDL-C on coronary heart disease prognosis are limited and to the best of our knowledge, this is the first study to investigate the association between discordance of

Table 2 – Characteristics of patients with concordant and discordant LDL-C and NHDL-C

	LDL-C<NHDL-C n=38 (group 1)	LDL-C=NHDL-C n=112 (group 2)	LDL-C>NHDL-C n=48 (group 3)	p
Age (years) *	58.9±9.3	63.5±11.1	63.7±10.4	0.054
Gender (% male) [β]	73.7	70.5	81.3	0.369
Smoking (%) [β]	68.4	57.1	66.7	0.331
Hypertension (%) [β]	60.5	64.3	52.1	0.351
Diabetes (%) [β]	50.0	25.9	25.0	0.013 [a,b]
Dyslipidemia (%) [β]	50.0	35.7	33.3	0.221
Body mass index (kg/m²) *	27.9±6.2	26.2±4.5	25.1±4.1	0.376
Total cholesterol (mg/dl) *	200.8±40.5	182.8±44.7	180.9±30.8	0.044 [a,b]
LDL-C (mg/dl) [δ]	105.2(46.0)	115.7(46.8)	121.8(40.2)	0.053
HDL-C (mg/dl) [δ]	30.0(6.0)	35.0(9.0)	42.0(17.0)	<0,001 [a,b,c]
Triglyceride *	321.2±164.9	140.1±43.8	90.0±24.6	<0.001 [a,b,c]
NHDL-C (mg/dl) [δ]	158.5(37.0)	147.0(53.5)	141.0(42.5)	0.002 [a,b]
Mean GRACE (death) *** score *	114.5±29.5	98.7±22.1	112.0±30.3	0.029 [a,b]
Mean GRACE (death and MI) **score [δ]	133.4±41.5	104.3±31.1	127.0±46.9	0.008 [a,b]
TIMI risk score [δ]	3.0(2.0)	3.0(2.0)	3.0(2.0)	0.925
In-hospital mortality (%)	1(2.6)	2(1.8)	1(2.1)	-----
Mortality at sixth month(%) [β]	5.7	5,7	4.4	0.176
Cardiovascular events at sixth month (%) [β]	11.2	18.4	19.6	0.473

*Data are expressed as mean±standard deviation or median(interquartile range) for continuous variables and number (percentage) for categorical variables; *: One Way Anova, δ: Kruskal Wallis, β:Chi-square. LSD or Conover-Iman test was performed for the binary comparisons among the groups and the p value was set at 0.05. Significant differences were found between a: group 1 vs group 2, b: group 1 vs group 3, c: group 2 vs group 3. Statistically significant p-values are in bold.*

LDL-C and NHDL-C and widely used prognostic risk scores in MI patients.

Patients with AMI are heterogeneous in terms of clinical presentation, risk factors and prognosis. Identifying patients at higher risk for recurrent cardiovascular events and death after AMI is important to manage cardiovascular care. GRACE and TIMI risk scores are the most widely used risk scores for prediction of prognosis in AMI. In a study by Guler et al.,[20] lipoprotein(a) levels were higher in the group of patients with high GRACE score than in the group with intermediate or low GRACE score, and lipoprotein(a) was found to have an additional prognostic value over GRACE score in predicting one-year adverse outcomes in NSTEMI patients.[20] In the present study, we found that GRACE score is highest in the group with LDL-C<NHDL-C compared to groups with LDL-C=NHDL-C and LDL-C>NHDL-C. One of the reasons for low LDL-C and high NHDL-C is the

amount of remnant cholesterol and lipoprotein(a) in plasma. Increased remnant cholesterol is associated with increased incident coronary heart disease and all cause mortality in general population.[21,22] It is also associated with increased all-cause mortality in patients with ischemic heart disease.[23] On the contrary, in a study with AMI patients, remnant cholesterol was found to be associated with low mortality.[24] In our study, we didn't have data on patients' lipoprotein(a) levels and directly measured remnant cholesterol. However, TG was highest in the group with LDL-C<NHDL-C and TG is marker of remnant cholesterol.[25] Remnant cholesterol such as VLDL and IDL, as well as lipoprotein(a), is also atherogenic and associated with inflammation.[26,27] Increased atherogenicity and increased inflammation may be related to high GRACE score in discordant group with increased remnant cholesterol. In a recent trial, lowering TG provides additional mortality benefit in patients with cardiovascular disease and using statin.[28]

Study Limitations

This study has several limitations. It is a retrospective study and there is the possibility of bias from unmeasured cofounders. There is no absolute definition and standard cut-off values for the discordance of LDL-C and NHDL-C. Other limitations include small sample size and short duration follow up. Further large-scale prospective studies will be required to validate our results.

Conclusion

GRACE score was higher in discordant group with LDL-C<NHDL-C, but there is no difference regarding TIMI scores between discordant and concordant groups. Risk stratification in AMI is mandatory to guide its management and patients with discordant LDL-C and NHDL-C may represent a group with poor prognosis. Individuals with AMI and discordance may be the target of the most aggressive pharmaceutical interventions.

Author Contributions

Conception and design of the research: Eren M, Kurmus O. Acquisition of data: Eren M, Aslan T, Akbuga K, Tolunay H. Analysis and interpretation of the data: Eren M, Kurmus O, Aslan T, Akbuga K, Tolunay H. Statistical analysis: Eren M, Kurmus O. Writing of the manuscript: Eren M, Kurmus O. Critical revision of the manuscript for intellectual content: Kurmus O, Aslan T, Akbuga K, Tolunay H.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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