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An alternative marker of low-density lipoprotein cholesterol in coronary artery disease: non-high-density lipoprotein cholesterol

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Background/aim: Dyslipidemia is one of the most important risk factors for coronary artery disease (CAD), and low-density lipoprotein cholesterol (LDL-C) is used to measure dyslipidemia. Non-high-density lipoprotein cholesterol (non-HDL-C) seems to be an alternative parameter to LDL-C as it is not influenced by triglyceride (TG) levels. The aim of this study is to compare non-HDL-C and LDL-C levels as risk markers in CAD patients.

Materials and methods: One hundred and ten CAD patients and 42 individuals with normal coronary angiography results were included in this study. Patients were divided into 2 groups: TG < 200 mg/dL (n = 75) as group 1 and TG > 200 mg/dL (n = 35) as group 2. Total cholesterol (TC), TG, and HDL-C levels were analyzed with a Roche Modular P800 autoanalyzer. LDL-C and non-HDL-C levels were calculated.

Results: There were statistically significant differences in TC, TG, HDL-C, and non-HDL-C levels when the groups were compared. Non-HDL-C levels of group 2 were statistically higher than those of group 1 and the control group. There was no significant difference in LDL-C levels between the groups.

Conclusion: Non-HDL-C levels are better risk markers than LDL-C levels, especially in patients with TG > 200 mg/dL, and non-HDL-C levels should be taken into consideration when evaluating the risk of CAD.

Key words: Non-high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, coronary artery disease

1. Introduction

Atherosclerosis is a chronic degenerative inflammatory process that occurs in the intima layer of medium and large arteries. Atherosclerotic coronary artery disease is one of the most common causes of morbidity and mortality in developed countries (1). Age, sex, family history, diabetes, hypertension, dyslipidemia, smoking, obesity, sedentary lifestyle, and psychosocial factors can be considered as the main risk factors for atherosclerotic heart disease (2). Recent studies have identified the concentration of plasma triglyceride (TG) and triglyceride-enriched lipoprotein particles (3,4), the size of lipoprotein particles (5,6), apolipoprotein B (apo-B), lipoprotein a, homocysteine, and C-reactive protein (CRP) (7) as risk markers besides the main risk factors. Endothelial damage, oxidative modification of lipids, and inflammation are 3 main factors known to take part in the development of atherosclerosis. Lipids are the most important components of atheromatous plaque. The main source of cholesterol in the atherosclerotic plaque is the esterified cholesterol in low-density lipoprotein cholesterol (LDL-C). The main factors that determine the migration of lipoproteins into subintimal spaces are the molecular size of lipids and gradient degree (1). Although LDL-C is known as the major factor in the process of atherogenesis, the higher levels and the migration of triglyceride-enriched lipoproteins [very-low-density lipoprotein cholesterol (VLDL-C)], intermediate-density lipoprotein cholesterol (IDL-C), chylomicron remnant, and lipoprotein a into the subendothelial space through damaged vascular endothelium can also have an important role in the formation of atheromatous plaque (2).

In clinical practice, total cholesterol (TC) and LDL-C levels are used to follow up dyslipidemia and evaluate the cardiovascular risk (8). In some studies, non-high-density lipoprotein cholesterol (non-HDL-C) was reported to be

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a better dyslipidemia marker than LDL-C in coronary artery disease (CAD) risk evaluation and prediction (9–12). LDL-C levels are affected by high TG concentrations. Additionally, nonfasting blood samples can give incorrect measurements of LDL-C levels, whereas non-HDL-C levels are not influenced by nonfasting states (13).

In our study we aimed to compare non-HDL-C and LDL-C levels as risk markers in CAD patients who underwent angiography for diagnosis with different TG concentrations.

2. Materials and methods

2.1. Patients

The study population consisted of 152 patients who were admitted to the Ankara Numune Education and Research Hospital Cardiology Department between April and June 2012 with complaints of chest pains. The control group included 42 patients with normal coronary angiography results. One hundred and ten patients who had more than 40% stenosis in coronary arteries were diagnosed with coronary artery disease and composed the patient group. To compare markers at different TG concentrations, the patient group was separated into 2 subgroups according to their TG levels. Group 1 (n = 75) consisted of patients with TG levels < 200 mg/dL and group 2 (n = 35) consisted of patients with TG levels > 200 mg/dL. Biochemical measurements were performed in the Ankara Numune Education and Research Hospital Central Biochemistry Laboratory. This study was approved by the local ethics committee of Ankara Numune Education and Research Hospital (Date: 08.05.2013. Number: 2013 - 600).

2.2. Blood samples and measurement

Fasting venous blood samples were collected in 10-mL Vacutainer tubes (BD Vacutainer) in the morning after acceptance to the Cardiology Department and centrifuged at 1300 × *g* for 10 min after completion of clotting. TC, TG, and HDL-C measurements were performed by enzymatic colorimetric test technique in a Roche Modular P 800 autoanalyzer (Roche Diagnostics, Mannheim, Germany). LDL-C levels were calculated by Friedewald formula [LDL-C = TC − (TG/5 + HDL − C)] (14) if TG levels were <400 mg/dL. LDL-C levels were analyzed by a homogeneous enzymatic colorimetric test technique with a Roche Modular P 800 autoanalyzer (Roche Diagnostics, Mannheim, Germany) if TG levels were >400 mg/dL. Non-HDL-C levels were calculated by the following formula: non-HDL-C = TC − HDL-C (15).

2.3. Coronary angiography

All patients underwent selective coronary angiography through the femoral artery using a Judkins catheter (Shimadzu, 30 MHz, 35 mm cine film, 6–7 F guiding catheter). The left anterior descending artery (LAD) and circumflex artery (Cx) were assessed in at least 4 positions and the right coronary artery (RCA) was assessed in at least 2 positions. The lumen diameter and stenosis were measured with a calibrated guiding catheter. Angiographic images were assessed by 2 independent cardiologists who were blind to the clinical and laboratory findings of the patients. Any stenosis of ≥40% in at least 1 major coronary artery was considered as CAD.

2.4. Statistical analysis

The findings of this study were analyzed SPSS 18. The conformity of continuous variables to normal distribution was tested with the Kolmogorov–Smirnov test. The descriptive statistics of continuous variables were expressed as mean ± standard deviation for normal distributions and median (min–max) for nonnormal distributions. The presence of a statistically significant difference between the groups in terms of continuous variables was examined with the Student t-test for parametric and the Mann–Whitney U test for nonparametric variables. The presence of a correlation between the groups was determined by Pearson and Spearman rho tests. $P < 0.05$ was considered the threshold of statistical significance for all tests.

3. Results

TG and HDL-C levels were significantly different between the control and the patient groups ($P = 0.003$ and $P = 0.011$, respectively). No significant difference was found between the patient and the control group in the terms of age and TC, LDL-C, and non-HDL-C levels. Lipid parameters of the control group and patient group are listed in Table 1.

In the subgroup analysis, TC, TG, HDL-C, and non-HDL-C levels were found to be significantly different between group 1 and group 2 ($P = 0.008$, $P < 0.001$, $P = 0.006$, and $P < 0.001$, respectively). There was no significant difference in LDL-C levels, which is known to be an important risk factor for CAD. There was a statistically significant difference between group 1 and 2 ($P < 0.001$) in non-HDL-C levels (Figure). Non-HDL-C levels were found to be significantly higher in the patients that had TG > 200 mg/dL (group 2) when compared with the control group ($P = 0.001$), but there was no significant difference between the control group and group 1 ($P = 0.578$). Lipid profiles of patients (groups 1 and 2) and the control group are presented in Table 2.

In the patient group (n = 152), there was a positive correlation between TG and non-HDL-C ($r = 0.449$, $P < 0.001$). In group 1 (TG < 200 mg/dL; n = 75), there was a positive correlation between TG and non-HDL-C ($r = 0.576$, $P < 0.001$). In group 2 (TG > 200 mg/dL; n = 35), there was no correlation between TG and non-HDL-C ($r = 0.273$, $P = 0.112$).

Non-HDL-C levels were significantly correlated with TG, TC, and LDL-C levels ($r = 0.449$, $P < 0.001$; $r = 0.961$,

Table 1. Demographic characteristics and lipid parameters of patient and control groups.

	Control group (n = 42)	Patient group (n = 110)	P-value
Age (years)	57.3 ± 13.3	61.7 ± 13.2	0.06
Total cholesterol (mg/dL)	182.71 ± 36.99	183.7 ± 46.79	0.898
HDL-C (mg/dL)	48.57 ± 13.60	42.97 ± 11.33	0.011*
LDL-C (mg/dL)	111.5 ± 32.4	108.40 ± 38.69	0.64
Triglyceride (mg/dL)	119 ± 41.116	168.45 ± 100	0.003*
Non-HDL-C (mg/dL)	134.71 ± 34.71	140.77 ± 44.67	0.430

Data are presented as mean ± SD.
*: There is a statistically significant difference between groups (P < 0.05).

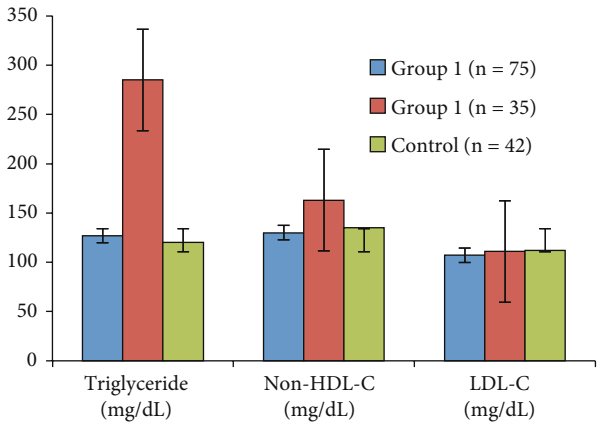

Figure. Triglycerides, non-HDL-C, and LDL-C levels in control group, group 1, and group 2.

Table 2. Lipid parameters of control group, group 1, and group 2.

	Control (n = 42)	Group 1 (n = 75)	Group 2 (n = 35)	P-value
Age (years)	57.3 ± 13.3	63.6 ± 13.5	57.8 ± 10.6	0.016
Total cholesterol (mg/dL)	182.7 ± 36.9	174.84 ± 45.3	202.8 ± 44.5	0.008[a,b]
HDL-C (mg/dL)	45 (16–80)	44 (17–77)	39 (22–62)	0.006[a,b]
LDL-C (mg/dL)	112 ± 32.4	107 ± 39.3	111 ± 37.7	0.803
Triglyceride (mg/dL)	117 (38–200)	112 (43–188)	243 (201–581)	0.000[a,b]
Non-HDL-C (mg/dL)	135 ± 34.7	130 ± 43.3	163 ± 39.5	0.000[a,b]

a: There is a statistically significant difference between group 1 and group 2.
b: There is a statistically significant difference between the control group and group 2.
Triglyceride and HDL-C values are presented as median (min–max); other parameters are presented as mean ± SD.

P < 0.001; and r = 0.928, P < 0.001, respectively). There was no correlation between HDL-C and non-HDL-C levels. Correlation analysis results between the parameters are shown in Table 3.

4. Discussion

Non-HDL-C levels are calculated by subtracting HDL-C levels from TC levels and are not affected by fasting state (8,13). Many studies have reported that apo-B and non-HDL-C levels are more valuable markers than LDL-C levels (16–18). Apo-B reflects total atherogenic particle load better than LDL-C because apo-B measurement includes LDL, IDL, lipoprotein a, VLDL, and VLDL remnants. Apo-B measurement is not used in clinical practice, but the use of non-HDL-C suggests an approximate idea about the level of apo-B (18). The Prospective Cardiovascular Munster Study (PROCAM) demonstrated a linear correlation between TG levels and the development of CAD, and the risk was increased especially when TG levels were >200 mg/dL (19). The ATP III guidelines also indicate high levels of TG as an independent risk factor for CAD (13). Non-HDL-C includes all of the potential lipoprotein cholesterol particles like LDL, VLDL, IDL, and lipoprotein a, which play a role in the process of atherosclerosis (20). Therefore, non-HDL-C can be defined as a more effective indicator for reflecting the risk of atherosclerosis compared with LDL-C. Another reason for non-HDL to be superior to LDL may be the analytical interference of LDL caused by high TG levels. The commonly used Friedewald formula as well as direct LDL measurements can be affected in high TG concentrations (21).

Some studies revealed that patients with diabetes and/or metabolic syndrome had larger amounts of small and dense LDL particles, and these patients had more atherogenic particle amounts than nondiabetic patients who had the same LDL-C levels. In the follow-up of these patients, non-HDL-C and apo-B concentrations become more important than LDL-C levels (22–24). ADA guidelines have recommended that non-HDL-C levels should be <130 mg/dL (calculated by 30 mg/dL addition to LDL-C levels) and apo-B levels should be <80 mg/dL for secondary prevention of cardiometabolic risk (25).

Table 3. Correlations between non-HDL-C and other parameters.

Non-HDL-C	r	P
Triglyceride	0.449	0.000
Total cholesterol	0.961	0.000
HDL-C	0.028	0.735
LDL-C	0.928	0.000

Laboratories measure TC, HDL-C, and TG, and then LDL-C is usually calculated by the Friedewald formula. When TG levels are above 400 mg/dL, LDL-C levels cannot be calculated correctly by this formula (15). Sequential ultracentrifugation methods or third-generation direct LDL reagents should be used to measure LDL cholesterol levels (26).

Gökçel et al. reported that LDL-C levels were well correlated with total cholesterol levels when TG levels were <400 mg/dL, and the correlation failed when TG levels were >400 mg/dL (27). Although LDL-C is preferred as a primary choice for therapy in dyslipidemia, the National Cholesterol Education Program suggests non-HDL-C as a secondary target in dyslipidemic patients with TG of >200 mg/dL (13). When TG levels are <200 mg/dL, a significant increase in VLDL-C levels may not be seen, and adding VLDL-C to LDL-C provides little advantage in the risk prediction of CAD. Non-HDL-C levels are highly correlated with LDL-C levels. When TG levels are >200 mg/dL, VLDL-C levels significantly increase and non-HDL-C levels alone reflect the concentrations of all atherogenic lipoproteins better than the levels of LDL-C (13).

In our study, especially in patients with TG levels of >200 mg/dL, non-HDL-C levels were better risk markers than LDL-C levels. In group 2, non-HDL-C levels were significantly higher than in group 1 (Table 2). There was no significant difference between group 1 and the control group in non-HDL-C levels. We believe that non-HDL-C can be used as an independent risk parameter when TG levels are >200 mg/dL. Even if LDL-C levels are normal, non-HDL-C levels can be considered as the target for treatment, and LDL-C and non-HDL-C levels can also be evaluated together when TG levels are <200 mg/dL.

Goliasch et al. studied lipid parameters in 102 myocardial infarction (MI) patients who were ≤40 years old. They reported that non-HDL-C levels were strongly associated with MI and that non-HDL-C levels can be used as a risk predictor and therapeutic goal in younger populations (28). Sigdel et al. also studied lipid parameters in patients with MI and in their study, non-HDL-C levels were more specific and sensitive than LDL-C levels (15). Garg et al. reported that metabolic syndrome is strongly associated with CAD and non-HDL-C levels are significantly correlated with metabolic syndrome. Non-HDL-C levels can be used in screening lipid-lowering therapy and CAD development risk (29). Uçar et al. included 2896 children (ages: 7–18 years) in their study and evaluated the prevalence of dyslipidemia. They reported that dyslipidemia prevalence was similar in terms of non-HDL-C levels and LDL-C levels. They found a positive correlation of non-HDL-C levels and TC, TG, and LDL-C levels and a negative correlation with HDL-C levels

(30). In our study, non-HDL-C levels were significantly correlated with TG, TC, and LDL-C levels. There was no correlation between non-HDL-C and HDL-C levels. Uçar et al. stated that non-HDL-C levels can be used to determine dyslipidemia in childhood (30).

Our study included an elderly population. Nearly one-third of all new coronary heart disease (CHD) events and about one-fourth of all CHD deaths occur in men aged 35–45. Age is defined as risk factor in CHD for women older than 55 and for men older than 45. Below these ages CHD is seen rarely if no other risk factors exist (13). We cannot evaluate the effect of age on non-HDL-C levels as we did not compare the results with a younger population. We think that our study population represents the population with risk factors better than a young population.

In conclusion, non-HDL-C can be preferred as a better risk marker than LDL-C, especially in patients with TG levels of above 200 mg/dL, and non-HDL-C levels should be taken into consideration when evaluating the risk of CAD.

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