Non-High-Density Lipoproteins Cholesterol and Cardio-Metabolic Risk

Dana BAIBATA; Georgiana IONESCU; Biliana PETCOV; Silvia MANCAS

a “Victor Babes” University of Medicine and Pharmacy, Timisoara, Romania
b Emergency Clinical Municipal Hospital, Timisoara, Romania

ABSTRACT
Background: The concept of cardio metabolic risk and risk stratification for cardiovascular events are two distinct entities related with different stages of vascular development of the atherogenic process. In our analytical transversal study, we analyzed non-high-density lipoprotein cholesterol behavior and the correlations with traditional cardiovascular risk factors in a subpopulation with coronary pain and indication of angio coronaryography. We tried to build a mathematical model in order to predict the non-HDLc, allowing additional cardiovascular risk reassessment.

Methods: We included 214 patients hospitalized for symptoms and signs suggestive of coronary artery disease and thus indication of vascular invasive evaluation. The protocol of the vascular evaluation included: assessment of cardiovascular risk for fatal cardiovascular event within the next 10 years, the lipidic risk profile, coronaryography and statistical analysis.

Results: We found a positive and highly statistically significant association between carotid artery intima-media thickness (c-IMT) and non-HDLc value (p <0.001). The mathematical model of linear regression showed the variability of non-HDLc depending on the following numeric variables: total cholesterol (TC), low density lipoproteins (LDL), triglycerides (TG), metabolic syndrome (MS); 97.5% of the non-HDLc variability was dependent on these variables.

Conclusions: Non-HDLc is a useful prognostic factor in cardio-metabolic risk quantification. The interdependent relation between non-HDLc and cardio-metabolic risk factors justifies the inclusion of this parameter in cardio-metabolic risk prediction equation in subjects with metabolic syndrome.

Keywords: non-HDLc, cardio-metabolic risk, metabolic syndrome, atherosclerosis
BACKGROUND

The concept of cardio metabolic risk and the risk stratification for cardiovascular events are two distinct entities related with different stages of vascular development of the atherogenic process (1).

The Canadian Cardio Metabolic Risk Study Group recently proposed using the concept of global cardio metabolic risk as a generic term in a comprehensive list of risk factors - the traditional and the new ones - predisposing to vascular injury and arterial remodeling (2). Changing the metabolic profile, mainly defined as cardio metabolic risk, is extremely complex. In this context, the European Society of Cardiology Guidelines for the management of dyslipidemias should include non-high density lipoproteins (non-HDLc) levels for cardiovascular risk screening (3).

Non-HDLc is a secondary target of therapy and its use is recognized in most guidelines in association to hypertriglyceridemia (Triglycerides-TG >200 mg/dl). The usefulness of using non-HDLc comes to the primary and secondary prevention, but also in those patients that reach the recommended low-density lipoproteins (very low density lipoproteins-VLDL, intermediate density lipoproteins- IDL, chylomicrons, triglycerides) (3).

In our analytical transversal study, we analyzed non-HDLc behavior and the correlations with traditional cardiovascular risk factors in a subpopulation with coronary pain and indication of angio-coronarography. We analyzed the association between, non HDLc levels and invasively determined coronary artery lesions. We then tried to build a mathematical model in order to predict the non-HDLc, thus allowing additional cardiovascular risk stratification.

MATERIALS AND METHOD

In our study we included 214 consecutive patients admitted to The Institute of Cardiovascular Diseases Timisoara between September 2012-May 2013; the selection criteria: anginal pain with indication for coronary angiography. The presence of coronary artery disease (assessed according to the invasive criteria) allowed the separation into 2 groups: A – subjects without coronary artery disease and B – subjects with certified coronary artery disease.

Both subgroups were characterized in terms of the following variables: age, gender, smoking status, body mass index (BMI), diabetes mellitus, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose, total cholesterol(TC), LDLc, HDLc, TG, non-HDLc. We assessed carotid morphology using ultrasound; the parameter used in our study was the carotid artery intima-media thickness (c-IMT), according to the American Society of Echocardiography Carotid Intima-Media Thickness Task Force recommendations (4).

We defined the following categories:

- overweight / obesity: according to body mass index (BMI): underweight BMI <18.5 kg/m², normal weight: BMI:18.5-24.9 kg/m², overweight: BMI: 25-29.9 kg/m², grade I obesity: BMI: 30-34.9 kg/m², grade II obesity BMI >35 kg/m² (5)
- Hypertension according to The European Society of Hypertension Guidelines: SBP ≥ 140 mmHg, DBP ≥ 90 mmHg (or medication)(6)
- Type 2 diabetes mellitus according to The Prevention Guidelines of the European Society of Cardiology: fasting plasma glucose ≥126 mg/dl or plasma glucose ≥198 mg/dL abnormal oral glucose tolerance test or treatment with oral anti-diabetic agents or insulin therapy (5)
- IDF metabolic syndrome criteria: waist circumference (WC) >80 cm (F), >94 cm (M), BMI ≥30 kg/m², BP ≥130/80 mmHg, fasting plasma glucose >100 mg/dl, TG >150 mg/dl, HDLc <50 mg/dl (F) and <40 mg/dl (M)

The lipidic profile (TC, TG, LDLc, HDLc, non-HDLc) was analyzed based on the criteria set out in the European Guidelines on Cardiovascular Disease Prevention in Clinical Practice of The European Society of Cardiology (5).

Statistical Analysis

Data obtained from our patients was collected in a Microsoft Excel file. The statistical analysis was performed using the SPSS 2010 Version 18 for Windows. The distribution of numerical variables was tested by the Kolmogorov-Smirnov test. In case of numerical variables with normal distribution, mean value and standard deviation were calculated, while
in case of non-normal distribution, median values and range intervals were used. The differences between numerical variables were analyzed by parametric (t-test) or nonparametric tests (Mann-Whitney or Kruskal-Wallis tests), according to the normal or non-normal distribution of the variables. Linear multiple regression was used to show non-HDLc variability depending on numeric variables.

RESULTS

We conducted a transversal study on 214 consecutive patients admitted for anginal chest pain and indication for coronaryography (mean age 61.48±8.76 years, 2/1 M/F ratio). According to the angiographical findings, we obtained 2 subgroups: A: without coronary artery disease (130 patients) and B: with coronary artery disease (84 patients).

The prevalence of coronary artery disease was 39.25%; 60.75% of the sample was at high cardiovascular risk and 39.25% at very high cardiovascular risk. Prevalence of risk factors in the studied group: 73.83% were hypertensive, 59% had high cholesterol, metabolic syndrome had a prevalence of 53.27%, smokers represented 50.93% of the group and 31% were diabetic.

The behavior of non-HDLc average values depending on the presence of symptomatic atherothrombotic cardiovascular disease showed statistically significant differences between the 2 groups: group A = 177.37±55.30 mg/dl vs. group B = 147.84±51.71 mg/dl, p <0.001 (Figure 1).

The degree of the dispersion values of non-HDLc in the entire sample is shown in Figure 2.

We obtained statistically significant positive correlation between the value of non-HDLc and the lipidic risk parameters (Table 1).

The analysis of the lipid risk factors profile showed statistically significant differences between analyzed groups (Mann-Whitney U test, 95% CI) (Table 2).

When we analyzed the relationship between non-HDLc and LDLc target recommended by the risk category, we obtained the following results: only 13.09% of subjects with coronary artery disease had reached the target LDLc <70 mg/dl. Mean non-HDLc in group B was significantly higher for those with ≥70 mg/dl LDLc (158.81±46 versus 75.01±14.02 mg/dl, p = 0.00005) (Figure 3).

In cases with coronary artery disease, 73.51% of the study participants had values of LDLc ≥100 mg/dl. For them, the mean non-HDLc value was significantly higher: 200.93±45.87 mg/dl versus 118.16±23.28 mg/dl (Figure 3).

We also found statistically significant differences for mean non-HDLc according to the presence of metabolic syndrome (170.87 versus 143.65±56.50 mg/dl 46.55 mg/dl p = 0.005) and hypertriglyceridemia (212.98±48.48 versus 150.63±49.09 mg/dl, p = 0.00002).

The mathematical model of linear regression showed non-HDLc variability depending on five numeric variables: TC, LDLc, TG, MS and c-IMT (Table 3).

The linear regression equation was:

\[
\text{Non-HDLc} = -24.89 + 0.476 \times \text{TC} + 0.492 \times \text{LDLc} + 0.123 \times \text{TG} + 3.66 \times \text{MS} + 3.96 \times \text{c-IMTstg}
\]

We therefore obtained a statistically significant model (p-value <0.001), with statistically significant coefficients (p-value <0.005) and a high value for the adjusted R^2 (0.975), which indicates that 97.5% of the variability of non-HDLc was explained by the variables in the model: TC, LDL, TG, and c-IMTstg, MS. In conclusion, the model was very good.

DISCUSSION

Our study about the non-HDLc behavior depending on the presence of traditional risk factors in a population-based set of patients with signs suggestive of coronary pain and indi-
only for a quarter of them. The patients with coronary disease presented lower values of non-HDLc and only 13% have achieved primary lipid target: LDLc.

Our results plead for at least three factors involved in the determinism non-HDLc: LDLc, TG and metabolic syndrome. These records with statistical significance justify aggressive prophylactic interventions to control the cardio-metabolic risk. It is estimated that non-HDLc is twice more powerful than LDLc in predicting risk reduction.

Another set of data highlights the quality non-HDLc as a predictor of subclinical atherosclerosis. Orakzai SH, Nasir K, Blaha M et al showed that non-HDLc is strongly associated with coronary artery calcification in asymptomatic individuals (6,7,8,11).

In our study, one third of the subjects with metabolic syndrome had cardiovascular disease certified by angio-coronarography. This proves the additional risk of metabolic syndrome for cardiovascular events.

It is now considered that non-HDLc and apoB are two parameters with predictive value for coronary events. The Emerging Risk Factors Collaboration, by analyzing 22 studies comprising 91,307 subjects, found for non-HDLc a HR: 1.59 (95% CI, 1.36-1.85) and for apoB a HR: 1.58 (95% CI: 1.39-1.79). The diabetic patients had non-HDLc values significantly higher than nondiabetic patients, while the LDLc values were within the target value. A post hoc analysis of the results from 4 large epidemiological studies - FCS (Framingham Cohort Study), FOS (Framingham Offspring Study), LRCF (Lipid Research Clinics prevalence follow-up) and MRFIT (Multiple Risk Factors Intervention Trials) discusses the value of non-HDLc as a marker of cardiovascular risk. Results from TNT (Treating to New Targets) support non-HDLc association with major cardiovascular event rates (HR: 1.14, p =0 .06) (9-12).

It is a reason to believe, based on the results of our study that the lipid risk reduction remains a key component in reducing the cardiovascular events: fatal / non-fatal.

Limitations of the study

Our study is an observational / analytical study, performed at some point in the evolution of the vascular atherogenic process. ❑
CONCLUSIONS

Non-HDLc is a useful prognostic factor in cardio-metabolic risk quantification. Non-HDLc was a marker of lipid risk both in patients with and without coronary artery disease.

The cut-off value for lipidic risk was exceeded in all analyzed subgroups. This clearly justifies the screening of non-HDLc and its aggressive management mainly in patients with elevated triglycerides.

The interdependent relation between non-HDLc and cardio-metabolic risk factors justifies the inclusion of this parameter in cardio-metabolic risk prediction equation in subjects with metabolic syndrome.

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TABLE 2. The relationship of non-HDLc with lipid risk parameters.

Model Summary

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a. Predictors: (Constant), TC
b. Predictors: (Constant), TC, LDLc
c. Predictors: (Constant), TC, LDLc, TG
d. Predictors: (Constant), TC, LDLc, TG, MS
e. Predictors: (Constant), TC, LDLc, TG, MS, c-IMTstg

TABLE 3. Non-HDLc linear regression model.

FIGURE 4. The correlation between non-HDLc and LDLc ≥100 mg/dl.


8. Arsenault BJ, Rana JS, Stroes ESG, et al. – Beyond low-density lipoprotein cholesterol: respective contributions of non–high-density lipoprotein cholesterol levels, triglycerides, and the total cholesterol/high-density lipoprotein cholesterol ratio to coronary heart disease risk in apparently healthy men and women. *J Am Coll Cardiol* 2010;55:35-41


