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Clinical Study

Relation of High-Density Lipoprotein Cholesterol and Apoprotein A1 Levels with Presence and Severity of Coronary Obstruction

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The aim of this work was to investigate the relationship between different lipids parameters with presence and severity of coronary obstruction angiographically evaluated. 897 patients (629 men and 268 women) underwent an angiography and blood extraction to determine concentrations of lipid markers: total cholesterol (TC), HDL cholesterol (HDLc), triglycerides, LDL cholesterol (LDLc), apolipoprotein A1 (apoA1), apolipoprotein B100 (apoB), non-HDL cholesterol and total cholesterol/HDLc, apoB100/apoA1 and LDLc/HDLc ratios. Multivariate analysis revealed that low HDLc levels were independently associated with the presence of coronary obstruction (OR: 0.982, 95% CI 0.969–0.996). In relation to severity of coronary stenosis, only apoA1 levels (OR: 0.990, 95% CI 0.980–1.000) and apoB/apoA1 ratio (OR: 3.243, 95% CI 1.095–9.608) were independent predictors. Our study demonstrated that HDLc was the only lipid parameter negatively and significantly associated with the presence of coronary obstruction, whereas apoA1 levels and apoB/apoA1 ratio were independent predictors of stenosis severity.

1. Introduction

Dislipidemia has been recognized as one of the major risk factors for coronary heart disease (CHD). Numerous studies have demonstrated the existence of a continuous and gradual relationship between hypercholesterolemia and total mortality due to ischemic cardiomyopathy [1, 2]. The role of LDLc in development and progression of atheromatous plaque has been clearly established in different experimental studies. Results of primary and secondary cardiovascular prevention studies with statins [3, 4] have focused attention towards modification of lipid profile through LDLc reduction. HDLc is an important prognostic factor of cardiovascular risk, so high values are associated with lower risk [5, 6].

Studies about the role of apolipoproteins as cardiovascular risk factors are more recent and showed an association of low apoA1 concentrations and high apoB with the pathogenesis of CHD [7, 8]. However, there is a great controversy to determine which one is the better discriminator of coronary risk. Some studies [7–10] have shown that apoB levels better reflect the number of atherogenic lipoprotein particles in a given volume of plasma considered that apolipoproteins quantification is better predictor of CHD risk than traditional lipid concentrations. However, other studies conclude that apolipoproteins A1 and B are not better predictors of coronary heart disease risk than traditional lipid measures [11–13].

The purpose of our study has been to investigate the relationship between different lipid parameters with the presence and severity of coronary obstruction angiographically evaluated.

2. Methods

2.1. Patients. 903 patients consecutively admitted in Basurto Hospital for angiography intervention by presenting an acute

coronary episode or to manage coronary heart disease have been studied. Angiography was conducted in all of them by femoral artery puncture, according to Seldinger technique. Patients were divided into two groups according to the result of angiography: Group 1, patients presenting a ≥50% diameter stenosis in at least one major coronary artery; Group 2, patients who had no significant obstructions. Patients in Group 1 were distributed into three groups according to the severity of coronary obstructions: Group A, patients with stenosis ≥50% in a vessel; Group B, patients with stenosis to ≥50% in two vessels; Group C, patients with stenosis greater ≥50% in three vessels.

During their stay in hospital, patients were given a questionnaire on their cigarette smoking and drinking habits, clinical history, and treatments for high blood pressure, dyslipidemia, and diabetes. Their weight and height were taken to calculate body mass index (BMI).

Patients with dyslipidemia were defined as patients with abnormal lipid levels in the first or previous analysis and who were under treatment. Hypertensives were patients with high blood pressure levels on admission to hospital or who were under hypertensive treatment regardless of current blood pressure levels. The diabetes group was defined as patients with basal glucose levels > 126 mg/dL or under diabetic treatment regardless of current glucose levels.

The study protocol was accepted by the clinical trials committee of the Hospital and explained to the patients, who freely agreed to be included in the study, signing the informed consent approved by the committee.

2.2. Laboratory Methods. Nonfasting blood samples were obtained prior to angiography, and the following parameters were analyzed: total cholesterol (TC), triglycerides, HDLc, LDLc, apoA1, and apoB. Total cholesterol, triglycerides, and HDLc were identified by routine enzymatic methods using a Hitachi (Roche Diagnostics) autoanalyzer. LDLc was calculated using the Friedewald's formula, and non-HDLc was calculated by subtracting HDLc to total cholesterol. ApoA1 and B100 were analyzed by immunoturbidimetric methods (Tina-quant), with a measurement interval of 20–400 mg/dL, and an interseries CV for apoA1 of 2.4% (x = 40 mg/dL) and 1.6% (x = 176 mg/dL), and for apoB of 2.5% (x = 29 mg/dL) and 1.1% (x = 112 mg/dL).

2.3. Statistical Analysis. Values of laboratory parameters, including lipid ratios (TC/HDLc, LDLc/HDLc, apoB/apoA1) were expressed as means and standard deviations. Student's t-test and ANOVA test were used to assess quantitative differences between variables. Spearman correlation coefficient was used to determine the relationship between lipid parameters.

A multivariate logistic regression model was constructed to determine the independent contribution among traditional risk factors and lipid variables to presence and severity of coronary obstruction. We first constructed a basic clinical model using logistic regression to identify the factors associated with the presence and severity of coronary artery disease. Next, the parameters found to be significant by univariate analysis were added in successive steps to see which ones proved to be independent predictors of the presence of coronary obstruction. In all cases, a P value ≤ 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS v17.5 software package.

3. Results

Of the 897 patients included in the study (620 were men and 268 women), 659 patients (73.50%) presented obstructive CHD for at least 50% in a vessel, and 238 patients (26.50%), with nonsignificant obstruction, were considered as controls.

Comparing clinical and demographic characteristics of both groups (case and controls), not statistically significant differences in age (65.46 ± 11.38 versus 64.13 ± 10.83 years) and BMI (3.87 ± 27.76 versus 28.20 ± 3.87 kg/m^2) were found. On the contrary, sex (75.4% men versus 55.5%, P < 0.001), tobacco (27.2% smokers versus 19.9%, P < 0.029), dislipemia (64.9% versus 47.9%, P < 0.001), hypertension (62.3% versus 53.2%P < 0.016), and diabetes (34.3% versus 22.2%, P < 0.001) showed differences statistically significant.

Table 1 shows the distribution of lipid parameters. TC/HDLc ratios, LDLc/HDLc, and apoB/apoA1 are positively associated with coronary obstruction, while apoA1 and HDLc are related with a decreased risk of coronary artery blockage.

We found a strong correlation between TC and LDLc (r = 0.931), TC and apoB (r = 0.810), TC and non-HDLc (r = 0.942), LDLc and apoB (r = 0.844), LDLc and non-HDLc (r = 0.948), and apoB and non-HDLc (r = 0.887). HDLc presents the strongest correlation with apoA1 (r = 0.760).

Patients with coronary obstruction (659) were divided into three groups according to CHD severity. Clinical and demographic characteristics and distribution of lipid parameters are set out in Table 2. Significant differences were found in age (increases with CHD severity); prevalence of diabetes also increases with CHD severity but does not reach statistical significance. Concentrations of apo A1 and cHDL significantly diminished, in contrast TC/HDLc, and apoB1/apoA1 ratios increased without reaching statistical significance.

After adjusting for sex, smoking, hypertension, diabetes, dyslipidemia, HDLc, apoA1, TC/HDLc, LDLc/HDLc, and apoB/apoA ratios, multivariate analysis revealed that sex (P < 0.000), dyslipidemia (P < 0.001), diabetes (P < 0.004), hypertension (P < 0.002), and low HDLc levels (P < 0.01) were independently associated with the presence of coronary obstruction (Table 3). In relation to CHD severity, after adjusting for age, diabetes, HDLc, apoA1, TC/HDLc, and apoB/apoA1 ratios, the stepwise multiple regression analysis results showed that only age (P < 0.001), apoA1 (P < 0.048), and apoB/apoA1 ratio (P < 0.034) were independent predictors (Table 4).

Table 1: Distribution of lipid parameters in Group 1 (patients presenting a ≥50% diameter stenosis in at least one major coronary artery) and Group 2 (patients who had no significant obstructions).

	Group 1 ($n = 659$)	Group 2 ($n = 239$)	P
Lipids (mg/dL)			
Total cholesterol	182.84 (42.71)	188.12 (41.65)	NS
HDLc	44.35 (12.08)	48.75 (13.30)	0.001
Triglycerides	131.62 (90.43)	123.45 (61.19)	N.S.
LDLc	112.97 (36.40)	115.27 (35.65)	N.S.
apoB	99.94 (26.61)	99.18 (26.10)	N.S.
apoA1	132.37 (26.36)	141.21 (25.71)	0.001
Non-HDLc	138.69 (40.03)	139.37 (39.67)	N.S.
Ratios			
CT/HDLc	4.36 (1.33)	4.07 (1.17)	0.005
LDLc/HDLc	2.70 (1.07)	2.49 (0.95)	0.015
apoB/apoA1	0.78 (0.25)	0.73 (0.23)	0.003

HDLc: high-density lipoprotein cholesterol; LDLc: low-density lipoprotein cholesterol; apo: apolipoprotein.
Parametric variables are expressed as mean (standard deviations); P values for differences between the two groups were determined by Student's t-test.

Table 2: Basal characteristics and distribution of lipid parameters between groups A, B, and C (single, double, and triple vessel disease, resp.).

	Group A ($n = 228$)	Group B ($n = 254$)	Group C ($n = 177$)	P
Age (years)	63.40 (11.55)	66.39 (11.21)	66.92 (10.88)	0.002
BMI (kg/m^2)	28.14 (4.10)	27.70 (3.74)	27.45 (3.72)	NS
Smokers (%)	29.6	25.9	25.4	NS
Hypertension (%)	61.4	61.4	64.0	NS
Dyslipidemia (%)	61.9	68.3	63.6	NS
Diabetes (%)	31.3	32.1	42.1	0.051
Lipid parameters				
Non-HDLc	137.82 (38.22)	136.62 (38.90)	142.33 (43.41)	N.S.
TC/HDLc	4.25 (1.31)	4.28 (1.25)	4.53 (1.35)	0.097
LDL/HDLc	2.62 (1.06)	2.65 (0.99)	2.81 (1.10)	0.200
apoB/apoA	0.75 (0.25)	0.78 (0.25)	0.81 (0.26)	0.073

Group A: patients with stenosis ≥ 50% in a vessel; Group B: patients with stenosis ≥ 50% in two vessels; Group C: patients with stenosis ≥ 50% in three vessels; HDLc: high-density lipoprotein cholesterol; LDLc: low-density lipoprotein cholesterol. Quantitative variables are expressed as percentages; Pearson Chi-square was used to determine P values; quantitative variables are expressed as mean (standard deviation), P values were determined by ANOVA test.

Table 3: Association between traditional risk factors and lipid variables to coronary obstruction: multiple logistic regression analysis.

	OR	95% CI	P
Sex	2.809	1.931–4.086	0.001
Dyslipidemia	2.231	1.581–3.147	0.001
Diabetes	1.805	1.208–2.698	0.004
Hypertension	1.735	1.216–2.475	0.002
HDLc	0.982	0.969–0.996	0.010

OR: odds ratio; CI: confidence interval.

Table 4: Association between traditional risk factors and lipid variables to CHD severity: multiple logistic regression analysis.

	OR	95% CI	P
Age	1.046	1.024–1.069	0.001
apoA1	0.990	0.980–1.000	0.048
apoB/apoA1	3.243	1.095–9.608	0.034

OR: odds ratio; CI: confidence interval.

4. Discussion

Coronary heart disease is the leading cause of mortality in developed countries, being the obstruction of a coronary vessel by an atheromatous plaque the most common mechanism for stable angina, with the presence of a thrombus in episodes of instability. Many efforts are being made to determine what risk factors are more important to develop an ischemic stroke and so to schedule effective prevention strategies to identify people at risk prior to a new acute coronary episode.

As in other studies, we observe that prevalence of hypertension, diabetes, dyslipidemia, and smoking habit was significantly higher in patients with coronary artery occlusion. Also, LDLc, apoB, TC, and non-HDLc levels were lower in this group, possibly due to the fact that a large

number of them (60.2%) were in treatment with statins. HDLc and apoA1 concentrations were significantly lower in patients with coronary artery obstruction; this suggests the importance of HDLc and apoA1 in CHD development in patients with "desirable" concentrations of cholesterol. Barter et al. [14], in a study with 9770 patients, concluded that HDLc levels were the best predictor of cardiovascular events in patients in treatment with statins, even in patients with LDLc levels lower than 70 mg/d. Likewise, TC/HDLc, LDLc/HDLc, apoB/apoA1 ratios also showed statistical significance.

Our data showed a clear and significant association between severity of coronary artery stenosis, angiographically proved, and apoA1 concentrations: apoA1 concentrations decreased as the number of affected coronary vessels increased. Apolipoproteins are known to be potent coronary risk factors, but less evidence exists on its relationship to the severity of angiographically defined coronary arterial disease. Garfagnini et al. have reported that apoA1 and apoA1/apoB ratio are better than HDL cholesterol in assessing the severity of coronary damage [15]. Nissen et al. [16], based on experimental evidences about apoA1, performed the first clinical trial with weekly administrations of apoA1 Milano injections in patients with acute coronary syndrome. Forty-five patients receiving five apoA1 Milano infusions showed a statistically significant reduction of atherosclerotic coronary volume versus the control group. Low concentrations of apoA1 were independent predictors for presence and severity of CHD. Also, other studies have revealed a highly significant relationship between apoA1 and apoB levels and the number of stenosed coronary vessels [17, 18].

One limitation of our study is the method used to establish CAD severity; it is based on the observation of angiographic stenosis of the coronary lumen. Plaque accumulation in coronary arteries eventually leads to the obstruction of blood flow and angiographic stenosis. Angiographic studies have shown the prognostic value of stenosis severity; however, it has become clear that dynamic changes of coronary plaques residing in the vessel wall precede luminal stenosis and, therefore, better reflect the development of coronary artery disease. In fact, most plaques that eventually cause acute coronary syndromes (vulnerable plaques) are not severely stenotic before the acute event because early plaque development leads to expansion of the vessel wall (positive remodeling), thereby delaying luminal stenosis despite plaque accumulation. There is accumulating evidence that plaque characterization can be used in clinical practice. The overall plaque burden and morphology have prognostic value and can influence preventive treatment plans; serial observation of plaque burden allows recognition of disease progression or regression.

Our study demonstrated that, in a group of patients treated with statins, with a clear reduction of LDLc levels, HDLc was the only lipid parameter negatively and significantly associated with the presence of CHD, whereas apoA1 and apoB/apoA1 ratio were independent predictors of CHD severity. Lipid lowering therapy has limited to no effect on the level of HDLs however; in several studies, treatment with statins, at their most frequently used doses, results in an elevation in HDLc that varies between 3% and 12% in type IIA and type IIB hyperlipidemia. However, there are indications from recent literature that these effects may be to some degree phenotypic-specific.

The search for new strategies with distinct approaches to control these lipid parameters will contribute to the development of more effective antiatherosclerotic therapies for reducing cardiovascular events.

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