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The correlation of apolipoprotein B, apolipoprotein B/apolipoprotein A-I ratio and lipoprotein(a) with myocardial infarction

Research Article

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Abstract: Recent evidence shows that apolipoprotein (apo) B, apoB/apoA-I ratio and lipoprotein(a) are better indicators of coronary risk than the conventional lipid profile. The aim of this study was to evaluate the correlation of apoA-I and B, and lipoprotein(a) with myocardial infarction (MI). We performed a cross-sectional study including 208 patients (100 men and 108 women), with and without previous MI evaluated by coronary angiography. The severity of coronary heart disease was scored on the basis of the number and extent of lesions in the coronary arteries. Lipid levels were measured by the enzymatic method and apolipoprotein levels were measured by the immunoturbidimetric method. The MI group had higher plasmatic levels of lipoprotein(a) (0.37 ± 0.28 vs. 0.29 ± 0.23 g/L, $p<0.05$), apoB (1.13 ± 0.40 vs. 0.84 ± 0.28 g/L, $p<0.05$) and of the apoB/apoA-I ratio (0.77 ± 0.37 vs. 0.68 ± 0.20, $p<0.05$) compared to controls. The area under the receiver operating characteristic (ROC) curves (AUC) suggested a good reliability in the diagnose of coronary heart disease for the apoB/apoA-I ratio (0.756, $p<0.05$), apoB (0.664, $p<0.05$), lipoprotein(a) (0.652, $p<0.05$) and total cholesterol/HDL-cholesterol (0.688, $p<0.05$). Multivariate analysis performed with adjustments for cardiovascular risk factors, showed that the levels of lipoprotein(a), apoB and apoB/apoA-I ratio are significant independent cardiovascular risk factors. Our results indicate that there is an important relationship among high plasma apoB concentration, lipoprotein(a) concentration, the apoB/apoA-I ratio, and MI. We showed that the apoB/apoA-I ratio has a stronger correlation with MI than the total cholesterol/HDL cholesterol ratio. We therefore suggest using apoB/apoA-I ratio and lipoprotein(a) in clinical practice as a markers of MI risk.

Keywords: *Apolipoproteins B and A-I • ApoB/ApoA-I ratio • Lipoproptein (a) •Coronary heart disease*

1. Introduction

Total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) have been recognized as principle lipid risk factors. In order to make a proper evaluation of lipid-related risk, high-density lipoprotein cholesterol (HDL-C), non-HDL-Cholesterol (non-HDL-C) as well as triglyceride (TG) levels, and lipid ratios, such as total cholesterol/HDL-cholesterol (TC/HDL-C), should also be considered as guidelines [1-3].

Prospective studies have shown that plasma apolipoprotein B (apoB) concentration reflects the number of LDL-C atherogenic lipoproteins and, as such, can be a valuable predictor for coronary heart disease (CHD) [4]. In addition, apolipoprotein A-I (apoA-I) is more important than HDL-C content for biochemical pathways that make HDL-C anti-atherogenic, including the adenosine triphosphate binding cassette [5]. The apoB/apoA-I ratio has been shown to be strongly related to risk of MI, stroke and other cardiovascular

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manifestations, as shown in the Apolipoprotein-related MOrtality RISk (AMORIS) [6,7], INTERHEART [8] and EPIC-Norfolk [9] studies.

Recent studies have shown that high lipoprotein(a) [Lp(a)] plasma levels are an independent marker for atherosclerosis: they attenuate fibrinolysis through inhibition of plasminogen activation, and promote coagulation through alleviation of extrinsic pathway inhibition [10]. The elevated plasma level of Lp(a) is a good predictors of CHD [11]. The aim of this study was to evaluate the relationship between apoA-I and B, lipids, and Lp(a) as measures of the risk of MI.

2. Material and Methods

2.1. Patients and study design

We performed a cross-sectional study of 208 patients (100 men and 108 women) with and without MI, who were hospitalized in the Department of Internal Medicine, Coulommiers, France between May 2005 and December 2005. The study protocol was approved by the ethics committee of the hospital and fulfilled the directives of the Helsinki Declaration. All subjects gave their informed consent before participation in the study.

Among the 208 patients, 104 (50%) patients with a history of MI, as confirmed by clinical, cardiac enzyme, electrocardiographical, and coronary angiography international standards, [12-16] were included in the case group. The control group consisted of 104 patients (recruited from the same hospital) with no evidence of CHD but who presented with cardiovascular risk factors. They presented to the ambulatory section of our Department for metabolic screening. All patients were evaluated using the same protocol: medical history, physical examination, 12-lead electrocardiography, and 2D and Doppler echocardiographic examination.

Those persons with a history of MI within the last 3 months or undergoing major events during hospitalization (*i.e.*, neoplasia, inflammatory diseases, infections), surgical interventions in the past 2 months or subsequent dyslipidaemia as a result of hypothyroidism, nephrotic syndrome, or colestasis were excluded in order to eliminate major causes of secondary lipid profile alterations.

2.2. Blood sampling

Venous blood samples were obtained after 12 h of fasting, and samples for lipids, apolipoproteins A-I and B, and lipoprotein (a), were drawn without stasis into evacuated glass tubes containing 1/100 volume of 0.5 mmol ethylenediaminetetraacetic acid (EDTA)/L. Plasma was obtained by centrifugation at 1500 g for 15 min, and was measured in fresh samples.

2.3. Biochemical analysis

All patients had TC (total cholesterol), HDL-C (high density lipoprotein), LDL-C (low density lipoprotein), and TG (triglicerides) plasma levels analyzed by enzymatic tests performed by a Roche-Hitachi 911 analyzer. Non-HDL-C was calculated as the difference between TC and HDL-C (in mg/dL) [1-3]. The plasma concentrations of apoA-I, apoB, and Lp(a) were measured by immunoturbidimetry using the Roche/Hitachi Modular analyzer. All reagents and standard controls conformed with the International Federation of Clinical Chemistry primary standards [17-19].

2.4. Clinical variables

We recorded risk factors such as age, sex, family background of CHD, smoking, hypertension, diabetes mellitus, obesity, and dyslipidemia; all were defined in accordance to international rules [20-22].

Family history of CHD was defined by a history of premature coronary artery disease in first-degree relatives (having occurred in those relatives at age <55 years for men and <65 years for women). Active smoking was defined as smoking at least one cigarette per day within the previous two months.

Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg and/or reported use of antihypertensive medication [20]. The presence of diabetes at baseline was defined as fasting plasma glucose >110 mg/dL (6.1 mmol/L) or use of oral hypoglycaemia agents or insulin [21]. Obesity was defined according to body mass index (BMI) level: overweight, between 25-29 kg/(m)^2, obesity, >30 kg/(m)^2 [22]. To characterize dyslipidemia, we used the National Cholesterol Education Program's classification (NCEP-ATP III) from 2002 and the 2004 [1,3] adaptation. Dyslipidemia was defined as TC >200 mg/dL, HDL-C <40 mg/dL, LDL-C >100 mg/dL, TG >150 mg/dL and non-HDL-C >130 mg/dL.

2.5. Statistical analysis

We utilized parameters of descriptive statistics, such as dispersion and centrality indices (mean, median, standard deviation) and frequency tables. Inferential statistics for two qualitative variables were ascertained by the Chi square or Fisher Exact Test (according to the case). Numerical continuous data with normal distribution were processed by means of the Student or ANOVA Test (for two or more than two categories, respectively). Numerical continuous data that could not

Table 1. Characteristics of study patients.

Patient Characteristic	Case group (n=104)	Control group (n=104)	p-value
Mean age, years	63.66 (9.20)	58.05 (12.44)	<0.05
Women, n (%)	57 (54.81)	52 (49.52)	NS [a]
Body mass index , kg/m^2	29.75 (6.56)	28.97 (7.50)	<0.05
Family history of CHD, n (%)	27 (25.96)	15 (14.28)	<0.05
Obesity, n (%)	45 (37.50)	22 (20.95)	<0.05
Diabetes mellitus, n (%)	31 (29.80)	18 (18.09)	<0.05
Hypertension, n (%)	61 (58.61)	43 (40.95)	<0.05
Smoking status, n (%)	60 (57.69)	48 (45.71)	NS
Total Cholesterol level, mg/dL	200.65 (42.32)	180.24 (49.79)	<0.05
LDL-Cholesterol level, mg/dL	125.66 (41.21)	113.44 (46.64)	<0.05
HDL-Cholesterol level, mg/dL	45.88 (12.04)	53.22 (23.12)	<0.05
Non-HDL-Cholesterol level, mg/dL	148.42 (42.07)	134.35 (48.25)	<0.05
Triglycerides level, mg/dL	159.62 (82.54)	142.75 (61.73)	NS
TC/HDL-C ratio	4.47 (1.55)	4.03 (1.29)	<0.05
Apolipoproteins A-I, g/L	1.25 (0.27)	1.27 (0.36)	NS
Apolipoproteins B, g/L	1.13 (0.40)	0.84 (0.28)	<0.05
ApoB/ApoA-I ratio	0.77 (0.37)	0.68 (0.20)	<0.05
Lipoprotein (a), g/L	0.37 (0.28)	0.29 (0.23)	<0.05

a NS, not statistically significant

be approximated with normal distribution were analysed using the Mann and Whitney or the Kruskall-Wallis Test (for two or more than two categories, respectively). Chart facilities were chosen in conformity with the tests performed.

Logistic regression analysis was utilised for multivariate analysis with estimation of odds ratios (OR) and 95% confidence intervals (CI).

All analyses were adjusted for identified confounding factors.

To evaluate the abilities of the apoB/apoA-I ratio, Lp(a) and TC/HDL-Chol to predict MI, we constructed receiver-operating characteristic (ROC) curves and calculated the areas under the curves (AUROC) [23].

All data processing were performed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) for Windows 6.0. The results were considered statistically significant for $p< 0.05$.

3. Results

3.1. Patient characteristics

The characteristics were compared between cases and controls (Table 1). The mean age in both groups was higher in patients with MI (cases), with statistically significant differences. Cardiovascular risk factors, including hypertension, diabetes, obesity, smoking, and a familial history of CHD had a higher prevalence in the MI group than in controls (Table 1).

The characteristics of lipids and apolipoproteins in both groups are also given in Table 1. For the case group of patients, with previous MI, the mean values of all lipid fractions were higher than in controls.

3.2. Relationship between (apo) lipoproteins and extent of coronary heart disease

The severity of the disease, expressed as the number of stenotic coronary arteries, was significantly correlated with higher levels of Lp(a), apoB and of the apoB/apoA-I ratio (Table 2).

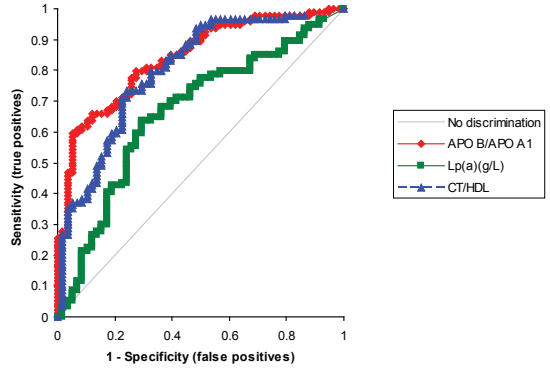
3.3. Receiver-operating characteristic for lipids and apolipoproteins analysis

Figure 1 shows the ROC analysis of TC/HDL-C ratio, apoB/apoA-I ratio and Lp(a) for detection of patients with future coronary artery disease. All AUROC were considered significant (p=0.001 for apoB/apoA-I ratio; p=0.020 for TC/HDL-C ratio; and p=0.032 for Lp(a). However, the AUROCs of the three markers did not differ significantly (0.688 for TC/HDL-C ratio; 0.756 for apoB/apoA-I ratio; 0.652 for Lp(a), p=0.653).

Table 2. Fasting lipids and lipoproteins in patients with 1-, 2-, and 3-vessel disease on coronary angiography.

Characteristics	1-vessel	2-vessel	3-vessel	p-value
Total Cholesterol level, mg/dL	178.13 (53.63)	190.77 (49.84)	191.25 (43.07)	NS
LDL-Cholesterol level, mg/dL	121.53 (35.42)	127.27 (31.44)	132.69 (33.87)	NS
HDL-Cholesterol level, mg/dL	43.12 (10.02)	41.98 (10.45)	37.52 (11.92)	NS
Non-HDL-Cholesterol level, mg/dL	132.78 (39.84)	142.51 (52.08)	145.72 (39.9)	NS
Triglycerides level, mg/dL	154.81 (70.84)	142.08 (70.91)	152.58 (75.93)	NS
TC/HDL-C ratio	4.39 (1.52)	4.62 (1.39)	4.73 (1.23)	NS
Apolipoproteins A-I, g/L	1.28 (0.21)	1.27 (0.24)	1.22 (0.25)	NS
Apolipoproteins B, g/L	1.13 (0.40)	1.26 (0.37)	1.35 (0.42)	<0.05
ApoB/ApoA-I ratio	0.77 (0.37)	0.98 (0.24)	1.12 (0.31)	<0.05
Lipoprotein (a), g/L	0.22 (0.23)	0.34 (0.20)	0.38 (0.25)	<0.05

Figure 1. Receiver-operating characteristic curves for the prediction of coronary heart disease.



3.4. Multiple regression analysis of association with the risk coronary

All lipid fractions and apolipoproteins were independent factors for MI risk in the univariate analysis. (Table 3).

Table 4 shows the multivariate analysis results, indicating the folowing factors as independent predictors: LDL-C (OR 1.69; 95%CI 1.12-2.27, p<0.05), TC/HDL-C ratio (OR 1.74; 95%CI 1.18-2.30, p<0.05), apoB (OR 2.38; 95%CI 1.63-3.13, p<0.05), Lp(a) (OR 1.88; 95%CI 1.63-3.82, p<0.05) and the apoB/apoA-I ratio (OR 3.26; 95%CI 2.27-4.25, p<0.05).

4. Discussion

In the present study we report the association between plasma apoB concentration and MI. A strong correlation with MI was also registered for the apoB/apoA-I ratio and for Lp(a) in the multivariate analysis, after adjustment for other cardiovascular risk factors.

Similarly to our data, the Québec study of 2155 men without CHD found a direct relationship between apoB and CHD prevalence (OR 1.4; 95%CI 1.2-1.7). Also, the apoA-I level in 116 subjects who developed CHD was lower than the apoA-I level in subjects without CHD. However, neither the apoA-I (OR 0.85; 95%CI 0.7-1.03), nor the apoB/apoA-I ratio contributed to the evaluation of coronary events risk after the adjustment for lipids, suggesting that apoA-I is not superior to the lipid profile as a predictor of CHD [4].

High plasma levels of HDL-C and apoA-I are inversely related to the risk of CHD [4,24]. The apoA-I level in our study represents a protective cardiovascular risk factor, as was found in the MONICA study, where apoA-I was inversely associated with coronary events [25]. In the IDEAL study, higher HDL-C proved to be a significant major cardiac event risk factor, following adjustment for age, gender, smoking, apoA-I, and apoB [26]. A similar association was observed for HDL particle size in EPIC-Norfolk [9]. In contrast, apoA-I remained negatively associated across the major part of its distribution in both studies [27].

The ROC analysis utilised in our study for the determining individual risk showed that apoB/apoA-I ratio had a better AUROC than the TC/HDL-C ratio, although both variables contribute to multivariate risk. Similar results were found in other studies, [6,9] which suggests that the apolipoproteins have a significant role in atherosclerosis as compared to “the traditional lipid profile.” The reason for the superior predictive ability of apoB/apoA-I ratio may be that the apoB serves as a marker for the number of atherogenic particles, because one apoB peptide is present on each particle.

Because of its strong genetic determination, the level of Lp(a) show small intra-individual variation, and apolipoprotein(a) polymorphism shows a significant association with cardiovascular events [28].

The Lp(a) determination method can itself induce various types of variations. Due to the dimensional variability of apo(a) isoforms, Lp(a) measurement cannot be precisely standardized based on mass concentration. Nor does immunodetermination provide a precise Lp(a) concentration level: This is a result of the

Table 3. Risk for future coronary artery disease, by lipid and apolipoproteins levels .

Characteristics	OR (95% CI)	p-value
Total cholesterol>200 mg/dL	2.04 (1.33-1.75)	<0.05
LDL-cholesterol >100 mg/dL	2.34 (1.12-3.56)	<0.05
HDL-cholesterol <40 mg/dL	0.73 (0.43-0.93)	<0.05
Triglycerides >150 mg/dL	2.21 (1.93-3.45)	<0.05
Non-HDL-Cholesterol >130 mg/dL	1.89 (1.78-2.76)	<0.05
TC/HDL-Cholesterol ratio >4.5	1.92 (1.36-1.88)	<0.05
Apolipoprotein A-I > 2.25 g/L	0.51 (0.10-0.92)	<0.05
Apolipoprotein B > 1.7 g/L	1.23 (1.11-1.56)	<0.05
Apo B/apo A-I ratio >1	3.57 (1.65-5.59)	<0.05
Lipoprotein (a) >0.3 g/L	**3.01 (1.62-5.51)**	<0.05

Table 4. Risk for future coronary artery disease, by lipid and apolipoproteins levels .

Characteristics	OR (95% CI)	p-value
Total cholesterol>200 mg/dL	1.15 (0.42-1.48)	NS
LDL-cholesterol >100 mg/dL	1.69 (1.12-2.27)	<0.05
HDL-cholesterol <40 mg/dL	0.64 (0.43-1.05)	NS
Triglycerides >150 mg/dL	1.24 (0.33-2.15)	NS
Non HDL Cholesterol >130 mg/dL	1.62 (0.48-2.76)	NS
TC/HDL-Cholesterol ratio >4.5	1.74 (1.18-2.30)	<0.05
Apolipoprotein A-I > 2.25 g/L	0.79 (0.66-1.05)	NS
Apolipoprotein B > 1.7 g/L	2.38 (1.63-3.13)	<0.05
Apo B/apo A-I ratio >1	3.26 (2.27-4.25)	<0.05
Lipoprotein (a) >0.3 g/L	1.88 (1.63-3.82)	<0.05

binding of measurement of antibodies to the structurally modified apo(a) epitopes. [29] Latex polyclonal apo(a) antibody determination has been replaced by the monoclonal antibody technique, due to its drawbacks: underestimation of Lp(a) plasma level in subjects with high apo(a) levels ,and overestimation of the Lp(a) plasma level in low-apo(a) plasma subjects. Therefore, modern research is based on either immunonefelometry or immunoturbimetry. Both methods have proven to have analytical variations: larger for immunonefelometry (5.8% to 13.3%), and smaller for immunoturbimetry (9.1%). We used the latter technique in our study, and therefore our results are subject to known variations [29]. Determination of Lp(a) using fresh plasma is considered to be the technique that greatly reduces the variation bias, and thus supports a high accuracy of the present study results. However, absolute cut-off values of Lp(a) need further validation and recalibration in larger studies.

With the above-mentioned limitations, our study indicates that a fresh plasma Lp(a) level over 0.30 g/L strongly correlates with MI risk, similar to other studies [30,31], suggesting that Lp(a) may have an significant role in atherosclerosis.

Accumulating evidence indicates that apoB, apoA-I and, especially, the apoB/apoA-I ratio, are strong predictors of risk for coronary heart disease, and are better markers than lipids for atherosclerosis and CHD [32-34]. The Apolipoprotein-related MOrtality RISk study showed that the apoB/apoA-I ratio was strongly related to increased risk for fatal MI (MI), and that plasma apoB and apoA-I levels and the apoB/apoA-I ratio were better predictors of risk than levels of total cholesterol or triglycerides [6]. Analysis of lipid variables in the Air Force/Texas Coronary Atherosclerosis Prevention Study population showed that baseline HDL-C, apoA-I, apoB, TC/HDL-C ratio and apoB/apoA-I ratio significantly predicted a first major acute event, whereas LDL-C and total cholesterol did not [35]. These studies have repeatedly shown that the cholesterol balance determined as the apoB/apoA-I ratio is a better marker than lipids and lipid ratios. These results taken together indicate that the apoB/apoA-I ratio is a simple, accurate and newly recognised risk factor for cardiovascular disease [36].

The present study had some additional limitations. First, case ascertainment is an issue in the design of a cross-sectional study. Second, in some subsets, because of the limited number of patients, we were unable to

make a strong case for true interaction between apoB, Lp(a) and lipids versus a simple multiplicative effect.

In conclusion, we showed that the apoB/apoA-I ratio was more closely associated with MI risk than was the TC/HDL-C ratio. High apoB and Lp(a) levels showed a higher correlation with future cardiovascular events as compared to "the traditional lipid profile." Thus, our data suggest that replacement of traditional lipid markers with the apoB/apoA-I ratio and Lp(a) in multivariate risk formulas may improve MI risk assessment.

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