Are apolipoproteins A and B better than lipoproteins for assessing risk of obstructive coronary heart disease?

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Objective – *To evaluate whether apolipoproteins A-I (Apo A-I) and B (Apo B) have, higher ensitivity (SN), specificity (SP) and positive predictive value (PPV) than lipoproteins (LP), total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), and triglycerides (TGL) in assessing the risk of coronary heart disease (CHD).*

Methods – *This is a transversal case-control study of 241 patients, who were divided into two groups: 1) 145 patients with CHD, and 2) 96 patients without coronary disease. A model of logistic regression to evaluate the relation between the LPs and CHD was developed in which variables with a p-alpha <0.1 were included.*

Results – *Apo A-I levels were higher in the patients without CHD, (OR 2.08, CI 1.20-3.57). There were no statistical differences between the values of Apo A-I and the remaining lipid fractions (Apo A-I: 67%; Apo B: 100%; PPV: TC= 71%; TGC=71%; HDL=71%; LDL=71%). The costs of the tests in Reais were as follows: Apo A-I: R$ 56.60; Apo B-100: R$ 56.60; TC: R$ 9.94; HDL: R$ 21.30; LDL: R$ 28.40; TGL: R$ 14.20.*

Conclusion – *Levels of Apo A-I and Apo B have no advantage over conventional lipoproteins in predicting the risk of CHD, despite the statistical association between Apo A-I and CHD; in addition, their costs are higher than those of the conventional lipoproteins.*

Keywords: risk factors, coronary heart disease, lipoproteins

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One of the major scientific contributions to cardiology in the last 40 years has been the identification of risk factors for coronary heart disease (CHD). One of these risk factors, elevated serum levels of cholesterol and other lipids, plays a major role in atherogenesis and its clinical manifestations. It was demonstrated that high density lipoprotein (HDL) cholesterol acts as an attenuating agent in atherosclerosis, whereas low density lipoprotein (LDL) cholesterol acts as an accelerator of that process and of clinical instability [1-13]. This knowledge allowed the adoption of measurable criteria for assessment of the risk of ischemic heart disease, using serum lipoprotein levels. These systematic experiences provided clinical trials that have aimed to reduce total cholesterol (TC) and LDL, and to increase HDL with thousands of patients. These trials showed that preventive measures to reduce cholesterol, with or without medication, significantly reduced clinical events and increased the possibility of reducing the atherosclerotic plaque [14-22]. The encouraging results of these investigations allowed the development of more specific research on other serum proteins. Among these, the investigation of apolipoproteins A (Apo A-I) and B (Apo B) aimed to the identification of more sensitive and/or more specific parameters for the prediction of the risk of ischemic heart disease stand out [23-60]. The results of this research disclosed discrepancies among the different centers conducting these studies. Some studies demonstrated that only Apo B was related to CHD while others showed that only Apo A-I was. In regard to the degree of sensitivity (SN) and specificity (SP), the different results also showed discrepancies.

Based on those previous studies, we designed this study with the following aims: 1) to assess the mean value of serum apolipoproteins in our population; 2) to evaluate whether Apo A-I or Apo B levels were higher in patients with CHD; 3) to compare SN, SP and the positive predictive value (PPV) of apolipoproteins with those of other lipids; 4)

to evaluate the applicability of measuring the apolipoproteins considering the cost-benefit ratio.

Methods

A transversal case-control study was carried out. This study comprised 308 patients with clinical and laboratory diagnosis of ischemic heart disease, who were referred to the catheterization laboratory of the Hospital das Clínicas de Porto Alegre (HCPA), from January 94 to June 96 for coronary angiography.

The patients were previously informed about the purposes of the study and also that their participation would not interfere with their treatment. Those who agreed to participate in the study signed a consent form that also authorized the withdrawal of 10mL of blood for further analysis and the copy of their electrocardiogram (ECG). Then, a semistructured interview was performed, in which the risk factors and comorbidities were assessed, including the use of medication and the current status of the ischemic disease. Sixty-seven patients were excluded from the study because of the following characteristics: recent (<3 months) acute myocardial infarction (AMI), use of thiadiazides in the last 2 weeks, use of lipid lowering agents, and other nonischemic heart diseases.

Cardiac catheterization was performed via the dissection of the right brachial artery or puncture of the right femoral artery, under local anesthesia (2% lidocaine); the selective study of the coronary arteries was performed using the techniques of Sones and Sinrey [61] or Judkins [62]. The coronary angiographic films were analysed by two researchers who did not know about the clinical and laboratory data of the patients. This interpretation consisted of direct visualization of the pattern and degree of the obstruction, and also the number of vessels affected by the disease.

Blood was withdrawn soon after reaching the arterial lumen and subsequently analyzed in the biochemistry unit of the HCPA. TC and TGL were analyzed by the colorimetric enzymatic method, using the Autoanalyser Selectra-Vitaldo. HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C) and VLDL-cholesterol (VLDL-C) were analyzed by the selective ionic precipitation/colorimetric enzymatic method, and Apo A-I and Apo B were analyzed by immunoturbidimetric assay and photometric measurement, with the turbiquant reagents [63-67].

To calculate the SNs, SPs and PPVs of the lipids, the standard values defined by the biochemistry unit of the HCPA were used as reference values. Altered biochemical values were considered a positive test and compared with coronary angiography, which was considered the gold standard, in which at least one coronary artery with an obstruction of 50% or more represented a positive test (group with disease). For the negative tests, only the cases with no obstruction in all arteries were selected (group without disease).

The reference values of apolipoproteins used as cutpoints were recalculated in the sample with aid of a ROC curve (not shown), and the values found were similar to those standardized at the biochemistry unit of the HCPA (table I).

The univariate statistical analysis was performed with Epi-info, version 6, and the multiple linear regression and the logistic regression were performed with SPSS, version 6.01. Age, sex, obesity, smoking, hypertension, diabetes mellitus (DM), TC, HDL-C, LDL-C, TGL and APO A-I and B were included in the regression model. The statistical power of the sample was 80% and the significant p-alpha was >0.05. The criterion of inclusion in the logistic regression model was p-alpha <0.1. For the model of logistic regression, the apolipoproteins were included in quarters and then separated in the following groups: Apo A-I <96mg/dL, between 96 and 111mg/dL, between 112 and 122mg/dL, and >122mg/dL. The same was done for Apo B and the groups were divided according to the following ranges: <101mg/dL, between 101 and 117mg/dL, between 118 and 132mg/dL, and >132mg/dL. The patients, divided into categories of those with and those without CHD, were then subdivided into those groups, according to their lipid profile.

Results

Of 241 selected patients, 145 had coronary atherosclerotic lesions ≥50%, constituting the group with CHD; the remaining 96 patients constituted the group without CHD.

The male patients comprised 60% of the sample. The mean age was 61.5 and 56.7 years, respectively for the groups with and without CHD; this difference was statistically significant (p=0.0009). Male patients predominated in the group with CHD (n=105) and females predominated in the group without CHD (n=57). This presentation had a strong statistical power (p=0.0000016) (fig. 1).

The Quetelet index also showed a significant variation in the groups with and without CHD (p=0.05).

DM was diagnosed in 44 patients, 68.2% of whom had CHD. Hypertension was diagnosed in 125 patients, 58.4% of whom had CHD. A family history was identified in 152 patients, 57.2% of whom had CHD.

Sixty-three patients were smokers, 76.2% of whom belonged to the group with CHD (odds ratio (OR) 2.67; CI 1.33-5.44). Once again the male gender stood out as a risk factor for CHD (OR 3.84; CI 2.13-6.93).

Table I – Reference values for cutpoints

Apo A-I	<116mg/dL
Apo B -male	>160mg/dL
female	>150mg/dL
Cholesterol	>200mg/dL
LDL	>130mg/dL
HDL	< 35mg/dL
VLDL	> 30mg/dL
TGL (30 years	>140mg/dL
31-40 years	> 150mg/dL
41-50 years	> 160mg/dL
> 51 years	> 170mg/dL

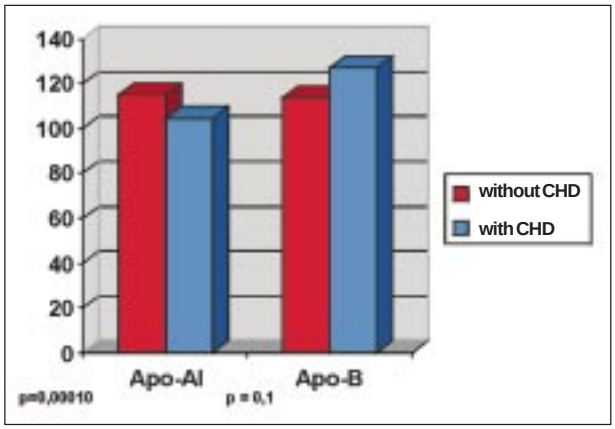

Fig. 1 – Concentration of apolipoproteins in patients with and without CHD.

The costs in Reais were as follows: Apo A-I R$ 56.60; Apo B R$ 56.60; TC R$ 9.94; HDL R$ 21.30; LDL R$ 28.40; TGL R$ 14.20.

Data showing the characteristics of the sample are presented in table II.

Apo A-I and Apo B had different behaviors in relation to the presence of coronary atherosclerosis. Serum levels of Apo B showed no significant statistical difference between the patients with and without CHD, neither by the analyses of the means nor by the laboratory reference values. Apo A-I, however, showed much lower serum levels in the group with atherosclerosis than in that without it, and the difference between these values was significant (p=0.0001).

In regard to TGL, TC and its lipoproteins LDL-C, HDL-C and VLDL-C, through the analysis of variance, statistically significant differences were observed between the patients with and without CHD. Significantly greater values of cholesterol, TGL, LDL-C and VLDL-C were observed in the patients with CHD, as well as reduced levels of HDL-C. Inverted values were found in the patients without CHD (table III).

Comparing the serum levels of the lipids and the presence or absence of CHD in the coronary angiography, SN, SP and PPV of each lipid were calculated, and the laboratory reference values were used to classify them as normal or altered. SN of Apo A-I for the presence of CHD in this group of patients was higher than that of the other lipid fractions with lower SP. However, its PPV did not statistically differ from the PPV of cholesterol, LDL, HDL, VLDL and TGL (table IV).

When observing Apo A-I values, one can see that, in the group without CHD, 30.5% of the patients had levels >122mg/dL; in the group with CHD, 35.4% of the patients had levels <96mg/dL; this association was statistically significant (p=0.0001). In regard to the values of Apo B, no significant relation with the presence of CHD was observed.

In a multivariate analysis using a model of logistic regression, where the variables sex, hypertension, DM, Quetelet index, smoking, age, and TC were controlled for, the relation proved to be significant for the levels of Apo A-I <96mg/dL and presence of CHD with OR 2.08 (CI 1.20-3.57). For the patients in our study, no other relation with the presence of coronary atherosclerosis could be demonstrated in this analysis (table V).

Table II - Characteristics of the sample

	With CHD	Without CHD
Total of patients	145	96
Sex: male (n=144)*	105	39
female (n= 97)*	40	57
Mean age (SD)*	61.5 (10.7)	56.7 (11.35)
Quetelet index (SD)*	26.27 (4.22)	27.38 (4.06)
Smokers (n=63) *	48 (76.2%)	15 (23.8%)
DM (n=44)	30 (68.2 %)	14 (31.8%)
Hypertension (n=125)	73 (58.4 %)	52 (41.6 %)
Family history of ischemic heart disease	87 (57.2 %)	65 (42.8 %)

p<0.05, chi-square.

Table III – Lipid profile: mean (standard deviation)

	Global Mean	Without CHD	With CHD
ApoA-1 p=0.00001	108.68 (21.74)	115.03 (20.65)	104.44 (21.48)
ApoB p=0.1	121.58 (55.8)	113.53 (23.8)	126.94 (68.95)
Cholesterol p=0.009	185.3 (40.74)	176.9 (39.08)	190.81 (41.02)
LDL-C p=0.017	121.38 (58.84)	119.26 (82.36)	122.81 (35.49)
HDL-C p=0.019	39.06 (10.62)	41.02 (10.64)	37.77 (10.44)
VLDL-C p=0.015	28.13 (14.71)	24.48 (14.42)	30.57 (14.44)
TGL p=0.0002	142.82 (84.77)	128.01 (97.62)	152.63 (73.81)

Table IV - Sensitivity, specificity and positive predictive values for lipids

Value	Sensitivity	Specificity	PPV
ApoA-1	66%	51%	66%
ApoA-1 male	64%	42%	73%
ApoA-1 female	68%	57%	55%
Apo B	06%	99%	90%
Cholesterol	41%	75%	71%
LDL	37%	76%	70%
HDL	48%	66%	68%
VLDL	42%	69%	67%
TGL	27%	83%	71%

Table V – Apo A-I and Apo B levels and the presence of CHD

Apo A-I p=0.0001	Without CHD	With CHD	OR*	CI (95%)*
>122mg/dL	29 (30.5%)	22 (15.3%)	1	
112-122mg/dL	26 (27.3%)	32 (22.2%)	0.81	0.48-1.37
96-111mg/dL	25 (26.4%)	39 (27.1%)	1.03	0.60-1.75
<96mg/dL	15 (15.8%)	51(35.4%)	2.08	1.20-3.57
Apo-B p=0.27				
<101mg/dL	29 (30.2%)	38 (26.2%)	1	
101-117mg/dL	21 (21.8%)	35 (24.1%)	1.06	0.62-1.86
118-132mg/dL	33 (34.4%)	38 (26.2%)	0.52	0.97-3.78
> 132mg/dL	13 (13.3%)	34 (23.5%)	1.71	0.87-3.39

*Multivariate analysis.

The SNs, SPs and PPVs of the lipids for the presence or absence of CHD varied according to the age of the patients. The measurement of Apo A-I had its peak of SN for CHD in the patients under 50 years of age and its higher SP in the age range from 50 to 59 years. TC showed a distribution similar to that of Apo A-I in these patients. PPVs in the patients over 50 years of age were equivalent (table VI).

Discussion

Even though the alterations in the metabolism of the TC, TGL, HDL, LDL, and VLDL are already well established risk factors for CHD, other lipid fractions were studied in an attempt to identify other more reliable biochemical parameters that can be universally employed to stratify the risk of CHD. These parameters should have reliable results with a small margin of error, be more economical or have better SN and SP than the dosages already well established. Among the new lipid fractions that have been studied, the studies with Apo A-I and Apo B stand out.

Our studies showed that the lipid profile as well as the other risk factors were similar to the Framingham studies [1,3,4]. Apolipoproteins levels were equivalent to those of other populations studied. In regard to the presence of CHD, using adequate statistical methods, we observed that the patients with CHD have lower levels of Apo A-I; Apo B levels were not statistically different from patients without CHD.

Sedlis et al [41], when relating CHD and apolipoproteins, found that the ratio Apo A-I/Apo B explains better the variation of CHD prevalence than the ratio LDL/HDL. However, when they compared the levels of Apo A-I in patients with and without CHD, no significance was found. The methodology they employed, however, was different from that employed in our study; in their study, patients with CHD were those whose score was ≥1, i.e., patients with 25% or more of obstruction in at least one artery, and without CHD those with 0 to 24% of obstruction, who scored no point. This may explain the differences found, because our study classified, as CHD, only patients with a stenosis of 50% or more in at least one artery, and without CHD those who had no obstruction at all.

Kwiterovich et al [54], who analyzed the relation between Apo A-I and premature CHD, found an association between Apo A-I and CHD in men, as well as between Apo B and CHD in women and the ratio Apo A-I/Apo B with significance for both sexes, but without any relation with isolated Apo A-I. Those authors defined as CHD the presence of stenosis greater than 50% in at least one artery and as absence of CHD those lesions ranging from 0 to 49%; once more, this may account for the differences with our study.

Fujiwara et al [57] compared CHD identified by coronary angiography with serum levels of apolipoproteins, lipids and insulin in nondiabetic patients. Based on 42 patients, they found that levels of Apo A-I and Apo B are the best lipid fractions to differentiate patients with and without CHD. In regard to Apo A-I, the results were similar to ours, even though they considered patients with CHD those with obstruction of more than 75% in at least one artery and patients without CHD those with an arterial stenosis of up to 25%.

Other studies analyzed the relation between the apolipoproteins and AMI. In a prospective study with an 8.6-year duration, Sigurdsson et al [55] analyzed the risk of AMI in different levels of Apo A-I and Apo B and other lipid fractions, and concluded that Apo A-I in men had a PPV, same risk as HDL, and the association of Apo B was not statistically significant. Even though this study did not use anatomical findings, its results were comparable to ours. Rubin et al [53], in an experimental study, showed that the higher levels of Apo A had no relation with the event AMI. In another study, Sewardsen et al [47] found an association demonstrating that Apo B was a better marker of CHD than the other lipid fractions, but they only analyzed normocholesterolemic nondiabetic Indian men. Analyzing the plasma from 246 patients with and without AMI, withdrawn 5 years prior to the event, Stampfer et al [49] found a relation between the high levels of Apo B, as a risk factor, and Apo A-I, as a factor for protection against AMI; in the multivariate analysis, this significance was lost. Kuyl and Mendelson [56], in an observational study, found no difference between the distribution of the ratios HDL/cholesterol and Apo A-I/Apo B, concluding that it added nothing to the dosage of these lipid fractions.

The analysis of SN, SP and PPV of the apolipoprotein and the other lipoproteins in our study shows that, even though Apo A-I had a higher SN than TC and LDL, its SP was lower and the PPV is similar. In regard to the HDL fraction, Apo A-I has a higher SN, lower SP and the same PPV. In regard to VLDL, it had a higher SN, same SP and same PPV. In regard to TGL, Apo A-I had a higher SN, a lower SP and a similar PPV (table III). Considering the prices of the exams, the costs in Reais were as follows: Apo A-I cost ranged from R$ 30.0 to R$ 56.80; HDL cost ranged from R$ 21.30 to R$ 48.00; and the TC cost ranged from R$ 8.40 to R$9.94.

Table VI - Sensitivity, specificity and PPV according to age

Age	Sensitivity	Specificity	PPV
<50 years			
Apo A-I	70%	30%	50
Cholesterol	45%	55%	64
50-59 years			
Apo A-I	62%	38%	69
Cholesterol	38%	62%	72
60-69 years			
Apo A-I	68%	32%	73
Cholesterol	41%	59%	72
> 69 years			
Apo A-I	65%	35%	71
Cholesterol	44%	56%	75

Considering the small advantage of Apo A-I compared to TC in regard to SN, SP and PPV and its high cost, we found no advantage in using Apo A-I as a factor of identification of risk for coronary atherosclerosis. Considering the other lipoproteins, Apo A-I could replace the HDL, LDL and VLDL fractions because of its higher SN and similar costs.

Based on the methodology employed in this study and considering its limitations, we can conclude the following: 1) the levels of Apo A-I and Apo B in the population of Porto Alegre are equivalent to the levels identified in other populations; 2) patients with obstructive coronary heart disease have lower serum levels of Apo A-I than those with no coronary artery disease; 3) the measurement of the levels of Apo A-I do not replace those already well established tests for the stratification of the coronary risk and its cost is higher; 4) serum levels of Apo B did not differ in the groups with and without coronary heart disease.

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