Apo B/Apo A-I Ratio in Central and Peripheral Arterial Diseases

perspectiva

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ABSTRACT

Background: The apo B/apo A-I ratio represents the balance between atherogenic particles, rich in apo B, and the antiatherogenic ones, apo A-I rich. This study investigated the association between atherosclerotic diseases in different anatomical sites and apo B/apo A-I ratio. **Methods:** Lipids, lipoproteins, and apolipoproteins A-I and B were assessed in 30 subjects with coronary artery disease (CAD), 26 with ischemic stroke (IS), 30 with peripheral arterial obstructive disease (PAOD), and 38 healthy subjects (controls). **Results:** HDLc and Apo A-I were significantly lower in PAOD and CAD groups, respectively, than in other groups. Significantly higher levels of triglycerides were observed for CAD and PAOD groups than for controls. Apo B was significantly higher in IS group than in control and PAOD groups. The apo B/apo A-I ratio showed significantly higher in CAD and IS groups when compared to control and PAOD groups ($p < 0.001$). **Conclusion:** The apo B/apo A-I ratio was important for identifying an increased trend for coronary and cerebral atherosclerosis. In spite of the increased trend for apo B/apo A-I ratio in IS and CAD groups, the studied variables cannot be considered in an isolated way, given as those parameters were analyzed together by a binary logistic regression, no association has been demonstrated. **(Arq Bras Endocrinol Metab 2007;51/7:1160-1165)**

Keywords: Apolipoproteins A-I and B; Coronary artery disease; Ischemic stroke; Peripheral arterial obstructive disease

RESUMO

Índice Apo B/Apo A-I nas Doenças Arteriais Central e Periférica.
Introdução: O índice apo B/apo A-I representa o balanço entre partículas de colesterol potencialmente aterogênicas ricas em apo B e partículas anti-aterogênicas ricas em apo A-I. O objetivo deste estudo foi investigar a associação entre doenças ateroscleróticas em diferentes sítios anatômicos e o índice apo B/apo A-I. **Métodos:** Lípides, lipoproteínas e apolipoproteínas A-I e B foram quantificados em 30 indivíduos apresentando doença arterial coronariana (DAC), 26 com acidente vascular cerebral (AVC), 34 apresentando doença arterial obstrutiva periférica (DAOP) e 38 indivíduos hígidos (grupo controle). **Resultados:** HDLc e apo A-I apresentaram-se significativamente mais baixos nos grupos DAOP e DAC, respectivamente, quando comparados com os demais grupos. Níveis de triglicérides foram significativamente mais elevados nos grupos DAC e PAOD quando comparados com o grupo controle. Apo B foi significativamente mais elevada no grupo AVC quando comparado com os grupos controle e DAOP. O índice apo B/apo A-I se mostrou significativamente elevado nos grupos DAC e AVC quando comparados com os demais ($p < 0,001$). **Conclusão:** O índice apo B/apo A-I foi importante para identificar uma tendência aumentada para aterosclerose coronariana e cerebral. No entanto, os parâmetros avaliados não podem ser considerados de forma isolada, considerando que nenhuma associação foi demonstrada quando os dados foram analisados pelo modelo de regressão logística binária. **(Arq Bras Endocrinol Metab 2007;51/7:1160-1165)**

Descritores: Apolipoproteínas A-I e B; Doença arterial coronariana; Acidente vascular cerebral; Doença arterial obstrutiva periférica

ATHEROSCLEROSIS IS, IN PART, a chronic inflammatory process involving the formation of atheroma plaques that may suffer rupture or erosion, thus provoking the thrombus formation (1). Among the most important thrombotic events are myocardial infarction (MI), ischemic stroke (IS), transient ischemia, and peripheral arterial obstructive disease (PAOD) (2). Epidemiological, clinical, and therapeutical studies show evidence of a correlation between the alteration in the lipid profile and atherosclerosis (3). However, a large number of patients who develop atherosclerotic diseases present normal lipid levels (4), demonstrating that, despite the enormous contribution of the dyslipidaemias to the development of atherosclerosis, other factors are also responsible for its progression.

Apolipoproteins A-I and B plasma levels have been described as better predictors of atherosclerotic diseases than the lipid and lipoprotein concentrations (5,6). The apo B/apo A-I ratio represents the balance between atherogenic particles, rich in apo B, and the antiatherogenic ones, apo A-I rich, and it has been shown to be a better parameter for the prediction of cardiovascular risk than the lipids, lipoproteins, and lipid ratios (7-10). Moreover, the apolipoproteins concentrations suffer little influence from biological variables when compared with lipid measurements (11-13). In contrast to the large number of studies demonstrating the predictive value of the apo B/apo A-I ratio for CAD, few studies have examined this index in other arterial ischemic events. Therefore, the relationship between the apo B/apo A-I ratio and IS and PAOD diseases is still not established.

This study explored the correlation of atherosclerotic diseases in different anatomical sites with apo B/apo A-I ratio in an attempt to encounter possible associations between clinical and biochemical abnormalities. The apo B/apo A-I ratio was also used to investigate the possible differences among patients with different risk factors, i.e., it was applied to establish a comparison between smoking and non-smoking patients, the presence or lack of hypertension, and the family history for atherosclerotic diseases.

MATERIALS AND METHODS

Patients and control subjects

The study protocol was approved by the Committee for Ethics in Research of the Federal University of Minas Gerais and the Committee for Ethics in Research of all the hospitals where patients were recruited. All subjects signed legal consent forms. Information on demographic characteristics, medical history and the presence of risk factors associated with atherosclerotic diseases, family history, and diagnostics of coronary and peripheral arterial disease were also assessed.

We assessed a total of 124 male and female subjects between the ages of 11 to 68 years. CAD patients, with coronary angiography demonstrating stenosis of more than 70 percent of the luminal diameter in one or more coronary arteries, were selected in the Socor Hospital in Belo Horizonte, Minas Gerais, Brazil. IS patients were selected in the University Hospital, Federal University of Minas Gerais, Belo Horizonte, the diagnosis being confirmed by magnetic resonance or computer brain tomography. Patients with PAOD were selected in the Santa Casa Hospital of Belo Horizonte. Their diagnoses were confirmed through clinical examination and measurement of the ankle/arm index (those having values lower than 0.9 were selected) (14). Patients submitted to arterial revascularization surgery in the lower limbs were also included. The control group was composed of healthy subjects with no previous history of CAD, IS or PAOD, selected in the hospitals where patients were recruited. On the basis of clinical criteria, the subjects were divided into four groups: control (n = 38), CAD (n = 30), IS (n = 26), and PAOD (n = 30).

Subjects with renal, hepatic, autoimmune, and mieloproliferative diseases, coagulation disorders and cancer, and those in a post-operative period or immobilized during a long time, or under lipid-modifying therapy were excluded from the study. All participants with triglycerides levels above 400 mg/dL were also excluded. The patients selected for the study were diagnosed for arterial disease at least three months before the venepunction.

Smoking habits and the family history of atherosclerotic diseases were confirmed based on the recommendations of the III Brazilian Guidelines on Dyslipidaemias and Guidelines for Atherosclerosis Prevention (15). Individuals were classified as having DM2 if plasma glucose was equal to or superior then 126 mg/dL in the fasting state (performed in all subjects not previously diagnosed as having diabetes) or if individuals were receiving oral anti-diabetics or insulin (16). Hypertension was diagnosed if the systolic and/or diastolic blood pressure exceeded 140 and/or 90 mmHg or those under antihypertensive agents (17).

Samples collection

Venous blood samples were taken from all subjects after fasting for 12 hours. They were advised not to practice vigorous physical activity and to avoid ingestion of ethanol in the 24 and 72 hours, respectively, preceding blood collection, so as to obtain biological samples from patients presenting an equilibrated metabolic state. Ten milliliters of venous blood without anticoagulant were collected from each participant using Vacutainer® System tubes (Becton-Dickinson). Samples were centrifuged at 1.100 *g* for 15 minutes for rapid serum separation. Serum aliquots were stored at -70°C.

Laboratory measurements

Total cholesterol (TC) and triglycerides (TG) were determined by enzymatic colorimetric methods (Randox® Cholesterol CHOD-PAP and Randox® Triglycerides GPO-PAP,

respectively). HDLc was performed by the enzymatic elimination method (Randox® HDL Cholesterol Direct), and LDLc was estimated by the Friedewald equation.

The plasma apolipoproteins A-I and B levels were assessed using the immunoturbidimetry assay (BioTécnica®, Brazil, Apolipoprotein A-I and Apolipoprotein B, respectively) in a Cobas Mira Plus (Roche®) device as instructed by the manufacturer. In brief, the test samples are reacted with a specific antibody to human apolipoprotein A-I or B in a suitable buffer. The turbidity induced by the formation of immune complexes was measured at 340 nm, and the values were then calculated automatically from a known standard. All of the assay steps were performed automatically by the instrument. No significant cross-reactivity or interference from other biochemical parameters has been observed for the assays (BioTécnica, Brazil). The coefficient of variation was 2.67% and 2.29% for apolipoproteins A-I and B, respectively (BioTécnica, Brazil). A commercial control-serum was used to verify the assays performance.

Statistical analysis

Data were analyzed by Sigma Stat version 1.0 software system using one-way analysis of variance (ANOVA) followed by the Tukey test. Triglycerides levels, which not presented normal distribution, were analyzed after log-transformation of the data. Categorical variables (risk factors) were analyzed by the Chi-square contingency test. Pearson's correlation coefficient was used to measure the linear association between two continuous variables. The minimum size of the sample was defined using the coefficient of variation previously described in the literature, considering a ten percent of variation around the average and with a minimum number of twenty individuals in each group. Based on the described criterion, it was possible to verify statistical differences with a 5% level of significance. To investigate possible association between both risk factors and biochemical parameters and each disease (IS, CAD, PAOD) it was performed a model of binary logistic regression.

RESULTS

Baseline characteristics of the study participants

The characterization of the groups, including sex and age, as well as the risk factors associated with atherosclerosis diseases, number of subjects, and percentage of each variable, is presented in table 1. Patients with CAD and PAOD were significantly older than controls and IS patients. For the smoking parameter, a significant difference was obtained for PAOD group as compared to IS and CAD groups ($p < 0.001$), while CAD and PAOD groups showed a significant difference compared to the IS group ($p < 0.001$) for hypertension. Regarding family history of atherosclerotic disease, IS and CAD groups were significantly different from the PAOD group ($p < 0.001$). For diabetes mellitus, CAD and PAOD groups differed significantly ($p < 0.001$).

Biochemical analysis

Biochemical data are also presented in table 1 as means and respective standard deviations. There was no statistically significant difference between the groups for TC and LDLc. Significant differences for the control, IS, and CAD groups were observed relative to PAOD group ($p < 0.001$) for HDLc plasma levels. Significantly higher levels of triglycerides were observed for CAD and PAOD groups than for controls. Apo A-I plasma levels in patients with CAD differed significantly from the control, IS, and PAOD patients ($p < 0.001$). A significant difference was observed between the IS group in relation to control and PAOD groups ($p < 0.001$) for plasma apo B levels. The apo B/Apo A-I ratio in IS and CAD groups differed significantly from the control and PAOD groups ($p < 0.001$). However, as these results were analyzed by using a binary logistic regression model, no described parameter on table 1 appeared to be associated to development of IS, CAD or PAOD. The distribution of values of Apo B/Apo A-I ratios in the groups studied is presented in figure 1.

Apo B/apo A-I according to risk factors

The averages of apo B/apo A-I ratio were calculated for the four groups in the presence of risk factors. Significant differences between smoking and non-smoking patients in groups IS ($p = 0.03$) and CAD ($p < 0.01$) were observed. With respect to the other risk factors, no significant differences were observed for the apo B/apo A-I ratio in the groups studied.

Correlations between the biomarkers

There were positive correlations between apo B and LDLc ($r = 0.53$, $p < 0.0001$) and between apo A-I and HDLc ($r = 0.44$, $p < 0.001$), considering all 124 participants, as has been reported previously for the methods utilized (18). The apo B/apo A-I ratio showed positive and significant associated with apo B levels ($r = 0.91$, $p < 0.0001$), TC levels ($r = 0.63$, $p < 0.0001$), TG levels ($r = 0.51$, $p < 0.0001$), and plasma LDLc levels ($r = 0.50$, $p < 0.0001$). Negative correlation was also observed between apo B/apo A-I ratio and plasma apo A-I levels ($r = -0.49$, $p < 0.0001$). However, no significant correlation was observed between apo B/apo A-I ratio and HDLc levels ($r = -0.02$, $p = 0.8134$).

Table 1. Characterization of the studied groups according to sex, age, and biochemical parameters (expressed as mean and standard deviation) and presence of the risk factor (percentage).

	Control	IS	CAD	PAOD
n (M/F)	38 (18/20)	26 (10/16)	30 (17/13)	30 (14/16)
Age (years)	37 ± 17	31 ± 15	61 ± 10*‡	64 ± 13*‡
Smoking	—	8 (31%)	10 (33%)	23 (77%)‡§
Hypertension	—	10 (38%)	26 (87%)‡	24 (80%)‡
Family history	8 (21%)	8 (31%)	13 (43%)	23 (77%)*‡§
Diabetes mellitus	—	—	3 (10%)	17 (57%)§
TC (mg/dl)	179 ± 41	208 ± 61	203 ± 42	188 ± 45
HDLc (mg/dl)	47 ± 9	46 ± 11	47 ± 8	35 ± 11*‡§
LDLc (mg/dl)	111 ± 36	117 ± 53	123 ± 37	125 ± 38
TG (mg/dl)	102 ± 54	129 ± 71	165 ± 75*	166 ± 128*
Apo A-I (mg/dl)	151 ± 10	147 ± 10	125 ± 7*‡§	148 ± 14
Apo B (mg/dl)	70 ± 15	89 ± 21*¥	80 ± 16	69 ± 13
Apo B/Apo A-I	0.46 ± 0.1	0.62 ± 0.2*¥	0.64 ± 0.1*¥	0.47 ± 0.1

n = sample size, M = male, F = female, TC = total cholesterol, HDLc = HDL cholesterol, LDLc = LDL cholesterol, TG = triglycerides, Apo A-I = apolipoprotein A-I, Apo B = apolipoprotein B, IS = ischemic stroke, CAD = coronary artery disease, PAOD = peripheral arterial obstructive disease. Significant differences ($p < 0.01$) among the groups are represented by the symbols (*) vs. control, (‡) vs. IS, (§) vs. CAD, and (¥) vs. PAOD.

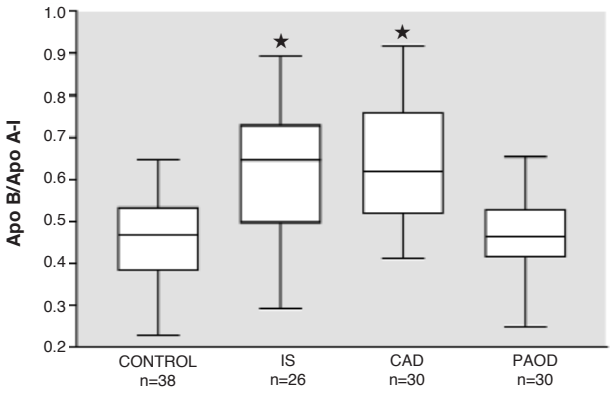

Figure 1. The distribution of the apoB/apoA-I ratios in controls, IS (ischemic stroke), CAD (coronary artery disease), and PAOD (peripheral arterial obstructive disease) groups. (★) Indicates significant difference in relation to the control and PAOD groups ($p < 0.001$). Each box represents the median and interquartile range of values, with the I bars (whiskers) extended to the minimum and maximum values.

DISCUSSION

Apolipoprotein metabolism is closely associated with the development of atherosclerosis, and the apo B/apo A-I ratio has been shown to be a better marker for prediction of cardiovascular events and prognosis than other classical lipid parameters such as TC and LDLc (19). In agreement, in the present study, the averages for TC and LDLc for all groups did not present significant differences (table 1). Thus, the above-mentioned parameters did not provide further information on the lipid alterations among patients with the three diseases.

The levels of HDLc were significantly lower in patients with PAOD than in patients with IS and CAD or in normal subjects. A possible explanation for this finding may be the fact that the PAOD group presented a high number of diabetic individuals (table 1). A high prevalence of dyslipidaemia in diabetic patients is described in the literature (16), and the association of the two conditions could aggravate the dyslipidaemia by synergism. TG plasma levels were significantly higher in CAD and PAOD groups than in the control group, but the latter had a lower mean age than the CAD and PAOD groups (table 1), a fact that may have contributed for such a finding.

This study demonstrated significantly lower apo A-I plasma levels for the apolipoprotein profile in the CAD group, when compared with the control, IS, and PAOD groups (table 1). Thus, the reduction in apo A-I levels correlated with the presence of CAD in the group of patients analyzed, while apo B did not provide further information. These data contribute for high apo B/apo A-I ratio showed for CAD patients. High apo B levels, as well as low apo A-I levels and a high apo B/apo A-I ratio, have consistently been associated with the CAD risk (9,19). Meisinger et al. (20) demonstrated a strong prediction of CAD by the apo B and the apo B/apo A-I ratio in men and women, while apo A-I did not contribute significantly for the coronary event in the MONICA/KORA study. On the other hand, according

to the Luc et al. (21) study, apo A-I has been shown to be an independent risk factor for CAD. Westerveld et al. (22) demonstrated that apo B plasma levels were superior to plasma levels of TC, HDLc, LDLc, TG, and apo A-I for predicting CAD in women. In the Kim et al. (23) study, only the apo B/apo A-I ratio was shown to be an additional tool for predicting CAD, when plasma levels of TC, LDLc, HDLc, apo A-I, and apo B were analyzed together in men and women with low risk for cardiovascular diseases.

In contrast to the vast literature available for the CAD risk, the association of apo B, apo A-I, and the apo B/apo A-I ratio in IS and PAOD is still not completely consolidated. Relatively fewer studies correlated these parameters with atherosclerotic diseases other than CAD. In this study, we found increased plasma apo B levels in IS group (table 1). Although apo A-I levels did not differ, the apo B/apo A-I ratio was significantly raised in patients with IS. Walldius et al. (24) recently reported a strong association between the apo B/apo A-I ratio and the risk of a fatal stroke, ischemic or not, in a prospective study involving a large number of subjects, suggesting that this association would be similar to that observed for MI.

All patients evaluated in this study had confirmed diagnosis of atherosclerotic diseases, but the apo B/apo A-I ratio was not significantly high in PAOD group. Contrasting to our findings, McConathy et al. (25) demonstrated that the apolipoproteins A-I and B differed significantly in PAOD from normal individuals in a group of women, when data was analyzed together with TC and TG dosages, while Schmidt et al. (26) demonstrated that the apo B/apo A-I ratio is associated with increased risk of cardiovascular diseases and femoral artery atherosclerosis as well, which showed to be a better marker than the LDLc. In the present study, the LDLc/HDLc ratio in PAOD group appeared significantly higher than in the other groups (data not shown), suggesting that for PAOD, the LDLc/HDLc ratio was more important than apo B/apo A-I ratio. However, it should be noted that PAOD patients were significantly older, smokers, and diabetics (table 1). In addiction, atherosclerotic plaques in PAOD have more fibrotic components than in CAD or IS, which presents more lipid components (27), what might partly justify this finding.

It was tempting, in spite of the small number of subjects, to check if the apo B/apo A-I ratio was associated with presence or absence of risk factors among patients. When patients were later grouped according to these criteria, a significant association was found between smoking and the apo B/apo A-I ratio in patients with IS and CAD. Indeed, the INTERHEART study (28) showed that the apo B/apo A-I ratio together with smoking explained 75% of the variability of the rate of acute MI worldwide. Although hypertension and family history are classical risk factors for atherosclerotic diseases (2), the fact that significant differences in apo B/apo A-I ratio were not found for hypertension or family history presence might be associated with the small sampling size analyzed in the present study.

It is of note the fact that apolipoprotein measurement presents some methodological advantages over the quantification of lipids and lipoproteins, as well as over the estimate of LDLc by the Friedewald equation (13). Apolipoproteins can be measured directly in the plasma by accurate, internationally standardized methods (11,12), and their values show small biological variation and small fluctuations in response to stimulation of metabolic control. Walldius & Jungner (29) suggested cut-off points of 0.9 and 0.8 for men and women, respectively, for the apo B/apo A-I ratio in the evaluation of atherosclerotic risk. Although significantly higher apo B/apo A-I ratios were detected in patients with CAD or IS than healthy subjects of the present study, the average values for apo B/apo A-I ratio detected were lower than these proposed cut-off points (table 1), according to MONICA/KORA study (20).

Because our observations are based on a small group of patients, it is difficult to propose a cut off value for apo B/apo A-I ratio to be taken as significant for each disease and would require a larger population analysis. Another important limitation is the fact that we evaluated only associations, not prediction or causation, and we could not explain why the HDL cholesterol and apo A-I values were reversed between the CAD and PAOD groups, since the cholesterol and protein components of HDL should track fairly closely. However, in the present data set, this did not occur. Finally, our finding is related to a group of patients not matched for age, a parameter that may affect apolipoprotein levels.

In conclusion, the apo B/apo A-I ratio was important for identifying an increased trend for coronary and cerebral atherosclerosis, in spite of the fact that heterogeneous distribution of apo B and apo A-I levels was observed among the different groups. In spite of the increased trend for apo B/apo A-I ratio in IS and CAD groups, the studied variables cannot be considered in an isolated way, given as those parameters were analyzed together by a binary logistic regression, no association has been demonstrated. Additional studies are required to extend the evaluation of apo B/apo A-I ratio in different populations and in different types of atherosclerosis events. Such studies may contribute for a more precise standardization of this parameter as a marker of atherosclerotic risk in different anatomical sites.

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