Apo B/Apo A-I Ratio and Cardiovascular Risk Prediction

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Apolipoproteins A-I and B

Apolipoproteins are proteins associated with lipids in lipoprotein particles. They play important roles in lipoprotein metabolism, such as transport of these hydrophobic molecules in plasma aqueous medium, binding to specific receptors in cell surface to correctly direct lipids to target organs and body tissues, and activation or inhibition of enzymes involved in lipid metabolism[1]. Apolipoprotein A-I (apo A-I) is the largest component of the high density lipoprotein (HDL) particle, representing approximately 45% of its molecular mass[2]. Moreover, it acts as a co-factor for the enzyme lecithin cholesterol acyl transferase and as a mediator in transfer of cholesterol from cells to HDL particles, which are important processes for the reverse transport of cholesterol to the liver[2]. Apolipoprotein B (apo B) is present in chylomicrons, such as apo B-48, and in very low density lipoproteins (VLDL), intermediate density lipoprotein (IDL) and low density lipoprotein (LDL), such as apo B-100, which is responsible for binding the lipoprotein to its specific tissue receptor[3]. Apo B is the main functional protein for transporting cholesterol to peripheral cells[4]. About 90% of protein in LDL is composed of apo B[5].

LDL, IDL and VLDL particles present an apo B molecule in their structure[3]; therefore, the plasma concentration of apo B indicates the total number of potentially atherogenic particles, correlating with the non-HDL cholesterol levels[6]. The plasma concentration of apo A-I is strongly associated with HDLc, and the expression of apo A-I may be responsible for determining HDLc plasma levels[6]. Hence, the apo B/apo A-I ratio represents the balance between apo-B-rich potentially atherogenic cholesterol particles and apo-A-I-rich antiatherogenic cholesterol particles.

Researches involving the predictive value of apolipoproteins A-I and B in atherosclerotic diseases emerged approximately two decades ago, initially as case-control studies[7-9] and, later, in prospective studies[10-12]. At present, plasma apolipoprotein A-I and B levels have been described as better predictors of atherosclerotic diseases than lipid and lipoprotein concentrations[6,13]; it has also been suggested that the apo B/apo A-I ratio represents a superior parameter for predicting cardiovascular risk as compared with other lipid ratios, such as total cholesterol/HDLc, LDLc/HDLc and non-HDL cholesterol/HDLc[14,15].

Key words

Apolipoproteins B; apolipoproteins A-I; prognosis; risk factors.

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Analytical considerations

Apolipoprotein measurements present some methodological advantages when compared with LDLc quantification. In most cases, LDLc is quantified by the Friedewald equation[16], which provides an estimate of the LDLc values and depends on total cholesterol, triglyceride and HDLc levels[17]. In this manner, the estimate may include the possible analytical errors of these three parameters used for calculating LDLc[6], thus increasing the likelihood of errors and of potential impact in clinical decisions[18]. This equation also presents several limitations and the LDLc estimate can not be extended to samples presenting triglyceride levels higher than 400mg/dl, samples containing chylomicrons and to patients with dysbetalipoproteinemia[19]. In addition, some studies have shown that the homogeneous method for measuring LDLc and the estimate of these values by the Friedewald equation do not show similar results[20-22].

On the other hand, apolipoproteins may be measured directly in plasma through accurate and precise internationally standardized methods[23,24], by using a common reference material for apo A-I and apo B which is not available for measurements of HDLc and LDLc, and without the significant interference of high triglyceride levels[18]. Plasma apolipoprotein levels are slightly influenced by biological variables, whereas plasma lipid levels fluctuate in response to various metabolic control stimulus[4]. Therefore preanalytical variables have less influence in the measurements of apolipoproteins A-I and B, which can be dosed with no need of prior fasting[11,12,25].

In Brazil, the operational costs related to apolipoprotein measures have considerably decreased in the past years with the introduction in the market of kits containing international-standard reagents made in the country. This fact enabled apolipoprotein A-I and B measuring by a larger number of clinical laboratories, at a more affordable cost to patients and payment by most health insurance plans.

Apo B/apo A-I ratio and coronary artery disease (CAD)

The predictive value of apolipoproteins A-I and B in CAD is well established and documented in the medical literature. High apo B levels, decreased apo A-I levels and increased apo B/apo A-I ratios have been consistently associated with risk of CAD[26-29].

Four recent prospective studies emphasized important evidence in the association between apolipoproteins A-I and B

and CAD. The Quebec Cardiovascular Study[10] assessed 2155 Canadian men and it was the first prospective study to show that apo B was superior to the conventional lipid ratios to predict cardiovascular risk. In the same study, after a 13-year follow-up[30], increased plasma levels of apo B remained as an independent risk factor for prediction of ischemic coronary events and the authors concluded that this association is higher in men with desirable levels of LDLc.

In an evaluation of 170 thousand Swedish individuals, the AMORIS (Apolipoprotein-related Mortality Risk)[11] study showed that apo B was a better marker of cardiovascular risk than LDLc, especially in individuals with desirable levels of LDLc, regardless of sex. The apo B/apo A-I ratio was identified in this study as the single variable that was more strongly associated with increased risk of fatal myocardial infarction (MI), particularly when lipid levels were within the range of desirable values. Other data obtained in this study[15] showed that the total cholesterol/HDLc ratio considerably underestimates the cardiovascular risk, and the apo B/apo A-I ratio was the best variable related to lipids to quantify coronary risk as compared with total cholesterol/HDLc, LDLc/HDLc and non-HDL cholesterol/HDLc ratios[14].

However, the INTERHEART[31] study evaluated about 30 thousand individuals in 52 countries and demonstrated that the apo B/apo A-I ratio was more strongly associated with MI prediction than several conventional risk factors, such as smoking, hypertension, diabetes, stress and abdominal obesity, regardless of sex, age and ethnicity. In the MONICA/KORA[32] study, 1414 men and 1436 women with no past history of MI were evaluated for 13 years. The main result of this study was the strong association between raised apo B levels and increased risk of MI, whereas increased apo A-I levels were not significantly associated with low risk of MI. However, the multivariate analysis showed that the apo B/apo A-I ratio was strongly associated with the risk of MI even after adjustments to age, body mass index, smoking, diabetes mellitus and hypertension.

Contrary to this study, the Women's Health Study[33], which evaluated 15000 women aged over 45 years for 10 years, revealed that the non-HDL cholesterol and the total cholesterol/HDLc ratio were as efficient as apolipoproteins A-I and B and the apo B/apo A-I ratio to predict cardiovascular risk. Nonetheless, apo B was the best single parameter to predict future cardiovascular events in women.

While some studies show the usefulness of increased apo B levels as predictors of cardiac risk[32,34], others have attributed this risk to diminished apo A-I levels[35]. But the consensus in the literature is still that the balance between atherogenic and antiatherogenic particles, reflected by the apo B/apo A-I ratio, represents an additional and important parameter for cardiovascular risk prediction, and nowadays it is considered a better marker when compared to lipids, lipoproteins and conventional lipid ratios[14,36].

Apo B/Apo A-I ratio and arterial disease in other anatomical sites

As opposed to the extensive literature available for CAD risk, the association between peripheral atherosclerosis and apo B/apo A-I ratio is not well established and this correlation has been described in few studies. In 1984, McConathy et al[37] showed that apolipoproteins A-I and B were important to differentiate individuals with peripheral occlusive arterial disease (POAD) from healthy individuals in a group of women, when the data were analyzed in conjunction with the measurement of total cholesterol and triglycerides. On the other hand, in a prospective study carried out by Schmidt et al[38] comprising 391 adult males who were followed up for 6.6 years, it was noted that the apo B/apo A-I ratio showed an association with atherosclerosis in the femoral artery and increased risk of cardiovascular diseases; this ratio behaved as a risk marker better than LDLc levels.

Two cross-section cohort studies conducted in our laboratory (unpublished data) showed controversial results in terms of the apo B/apo A-I ratio and peripheral atherosclerosis. In the first study, the apo B/apo A-I ratio was significantly increased in young patients with peripheral atherosclerosis at different anatomical sites (upper and lower limbs and retina) when compared with healthy individuals. On the contrary, in another study that evaluated elderly patients with peripheral arterial disease in lower limbs, the apo B/apo A-I ratio did not show any additional contribution when patients were compared with healthy individuals. In spite of the significant differences in the group composition (age, risk factors, affected anatomical sites, etc), these data reinforce the need of further studies involving the apo B/apo A-I ratio and peripheral atherosclerotic diseases.

As to atherosclerosis in cerebral arteries, evidence is recent and scarce. In a study by Bhatia et al[39] with 261 patients with previous transient ischemia and followed up for 10 years, the apo B/apo A-I ratio was the best independent predictor for ischemic stroke in this group of patients, followed by apo B, when the data were analyzed along with lipids, lipoproteins and traditional lipid ratios. This observation was confirmed by the AMORIS study[40] that showed a strong association between apo B/apo A-I ratio and risk of stroke, ischemic or not, suggesting that this association would be similar to that reported for CAD. The multivariate analysis of this latest study also established that the apo B/apo A-I ratio was a better risk predictor than the conventional ratios of total cholesterol/HDLc and LDLc/HDLc, thus representing a better marker of ischemic events.

Apo B/apo A-I ratio and lipid-lowering drugs

Some studies involving the apo B/apo A-I ratio revealed that lipid-lowering drugs, especially statins, have relevant effects on the apolipoprotein profile, some leading to significant reduction in apo B levels[41], others to increased apo A-I levels, and still other statins acting in both apolipoproteins[6,42,43]. Hence treatment with these drugs may present a great potential to correct the abnormal balance between atherogenic and antiatherogenic lipoproteins, which is closely associated with cardiovascular risk.

However, the use of apolipoproteins A-I and B and apo B/apo A-I ratio as treatment target for lipid-lowering drugs

has not been completely established in the literature. The inclusion of these parameters in the North American and European consensus for the prevention of cardiovascular diseases has been the object of controversy and debate among researchers in this area[44]. The greatest problem would be that, once the treatment goal for the apo B/apo A-I ratio is established, would it be better to decrease the numerator values (apo B) or increase the denominator values (apo A-I)? Evidences favoring the decrease of apo B levels are very strong[45,46], but the increase of apo A-I levels is also important to decrease the cardiac risk[28]. The benefits of lipid-lowering drugs in the apolipoprotein profile are not under discussion [see Ref 44], but a good cardiovascular risk marker does not necessarily have to indicate a treatment goal. Thus, increased apo B/apo A-I ratio can perfectly be used only as marker of increased risk and not necessarily as a target for therapy with lipid-lowering drugs.

Cut-off points

In 2004, Walldius et al[6] suggested cut-off points for the apo B/apo A-I ratio of 0.9 and 0.8 for men and women, respectively, showing that higher values would represent an increased risk of cardiovascular disease. These values have been confirmed by other researches[37,47,48] and the results of the AMORIS[11] and INTERHEART[31] studies established risk ranges for MI, which are shown in table 1.

Table 1 - Risk of MI in terms of increased apo B/apo A-I ratios

	Low risk	Moderate risk	High risk
Men	0.40 – 0.69	0.70 – 0.89	0.90 – 1.10
Women	0.30 – 0.59	0.60 – 0.79	0.80 – 1.00

Adapted from AMORIS[11] and INTERHEART[31] studies.

Conclusion

Based on recent evidence of the advantages of using apolipoproteins A-I and B as markers of cardiovascular risk, apo B/apo A-I ratio emerges as an important complementary parameter for the evaluation of this risk, especially in normolipidemic individuals, and it has potential importance in the future monitoring of high-risk patients receiving lipid-lowering drugs.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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