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ApoB/apoA-I ratio is better than LDL-C in detecting cardiovascular risk

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Abstract *Background and aims:* Cardiovascular (CV) events occur even when LDL-C are <100 mg/dL. To improve the detection of CV risk we investigated the apoB/apoA-I ratio versus LDL-C in subjects considered normal glucose tolerant (NGT) by oral glucose tolerance test (OGTT).

Methods and results: We enrolled 616 NGT (273 men and 343 women), and we measured insulin resistance, lipid profile, apoB/apoA-I and the factors compounding the metabolic syndrome (MetS). An unfavourable apoB/apoA-I (≥0.9 for males and ≥0.8 for females) was present in 13.9% of 108 patients with LDL-C <100 mg/dL: compared to subjects with lower apoB/apoA-I (<0.9 for males and <0.8 for females), they had more elements of MetS and their lipid profile strongly correlated with high CV risk. Out of 314 patients with lower apoB/apoA-I, 40.12% had LDL-C ≥130 mg/dL: these retained a more favourable lipid profile than corresponding subjects with elevated apoB/apoA-I ratio. Finally, we found a significant correlation between LDL-C and apoB/apoA-I ratio ($r = 0.48$, $p < 0.0001$).

Conclusions: In NGT with LDL-C <100 mg/dL, a higher apoB/apoA-I exhibited an atherogenic lipid profile, indicating that LDL-C alone is insufficient to define CV risk. Independent from LDL-level, when apoB/apoA-I is lower, the lipid profile is, in fact, less atherogenic. This study demonstrates that apoB/apoA-I is at least complementary to LDL-C in identifying the ''effective'' CV risk profile of asymptomatic NGT subjects.

Acronyms: CV, Cardiovascular; NGT, Normal glucose tolerant; OGTT, Oral glucose tolerance test; MetS, Metabolic syndrome; LDL-C, Low density lipoprotein Cholesterol; VLDL, Very low-density; IDL, Intermediate-density; HDL, High-density lipoproteins; NCPE, National Cholesterol Education Program; TG, Triglycerides; non-HDL-C, Non-HDL-cholesterol; HDL-C, HDL-cholesterol; 0′, Baseline; 2 hours, (2 h); Gly-0′, Baseline glycaemia; Ins-0′, Baseline, Insulinemia; Gly-2 h, 2 h glycaemia; Ins-2 h, 2 h insulinemia; WC, Waist circumference; HOMA, Homeostatic model assessment; M, Means; SD, Standard deviations.

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Introduction

The concentration of low density lipoprotein cholesterol (LDL-C) is generally accepted as being one of the strongest risk factors for atherosclerotic cardiovascular (CV) disease and mortality [1]. Although LDL-C is widely recognized as the major atherogenic lipoprotein, other lipoproteins are involved in atherogenesis, including very low-density (VLDL), intermediate-density (IDL), and high-density lipoproteins (HDL). Each class of lipoprotein particles is associated with distinctive apolipoproteins which, in addition to stabilizing lipoprotein structure, play an essential role in regulating lipid metabolism. ApoB, being present in VLDL, IDL and LDL, represents the total number of atherogenic lipoproteins [2,3]. ApoA-I is the major apolipoprotein associated with HDL and it is crucial in transferring excess cholesterol from tissues to the liver [3,4]. ApoB and apoA-I appear then to exert opposing effects on atherogenic risk, to the extent that the apoB/apoA-I ratio seems very effective in characterizing the CV risk [3–7]. Furthermore, this ratio has a stronger relationship with CV risk than any other lipid ratio [7,8].

Actually, based on data from large-scale intervention trials using statins [9,10], the National Cholesterol Education Program (NCPE) has proposed guidelines for lipid management that are continually being updated [11,12]. The current major treatment guidelines focus on LDL-C targets, taking into account individual patient's history and calculated risk profile [11,12]. The NCPE update suggests to reach LDL-C target of 100 mg/dL in ''high-risk individuals'' and recommends the use of non-HDL-cholesterol (non-HDL-C) as target for individuals with high triglycerides ($\geq$200 mg/dL).

Aggressive targeting of LDL-C with statins has been shown to reduce the incidence of CV disease by about one third. However a considerable proportion of patients with active atherosclerotic disease have levels of LDL-C within the recommended range, and some patients who achieve significant LDL-C reduction with lipid-lowering therapy still develop CV events [2,13,14]. Therefore, there is need for improving the cardiovascular risk assessment.

The analysis of epidemiological studies [3,5] indicates that the higher the apoB/apoA-I ratio, the higher is the CV risk, such that cut-off values $\geq$0.9 and $\geq$0.8 have been proposed to define a high CV risk for males and females, respectively [4,8]. Elevated levels of apoB are a component of the metabolic syndrome (MetS), a clinical condition where the presence of an atherogenic lipid profile, characterized by high triglycerides (TG) and low HDL-cholesterol (HDL-C) levels, is common [15]. Thus, the apoB/apoA-I ratio could be helpful in the clinical management of a very high CV risk syndrome where insulin resistance is widely believed to constitute a crucial pathogenetic factor [15].

In this study we investigate, in subjects with normal glucose tolerance (NGT), whether the apoB/apoA-I ratio could improve the detection of the CV risk profile with respect to the conventional cut-off LDL-C levels in relation to some clinical features of MetS, like insulin resistance and atherogenic lipid profile, each of them independently considered as a CV risk factor.

Methods

This study, conceived to verify the contribution of the apoB/apoA-I ratio, compared to the LDL-C levels, in defining the CV risk profile, was performed in a General Internal Medicine ward, affiliated with a Medical School, with an outpatients' facility for referrals targeted to arterial hypertension and/or metabolic abnormalities. After at least 5 days of a weight-maintaining diet (55% of calories from carbohydrates, 25% from fats, 20% from proteins) and avoidance of strenuous exercise, each non-diabetic subject undergoes an oral glucose tolerance test (OGTT) in which venous blood samples are drawn at baseline (0′) and 2 h (2 h) later for determination of glycaemia and insulinemia (respectively Gly-0′, Ins-0′; and Gly-2 h, Ins-2 h).

Inclusion criteria for this study were: normal physical examination and routine laboratory exams and normal OGTT, in accord to ADA 2003 [16]. Exclusion criteria were: abnormal OGTT, TG $\geq$400 mg/dL, evidence of liver, endocrine and renal diseases and/or a history of a previous or active CV disease, medications affecting glucose or insulin metabolism and/or a statin within the last six months. The study was designed in compliance with the ethics regulations set out by the Helsinki Declaration.

Out of 1168 subjects who underwent an OGTT from 2002 to 2008, 616 subjects, satisfying the inclusion criteria, were enrolled in this study, 273 males, 343 females (174 postmenopausal). Essential arterial hypertension was present in 387 of them.

For each subject enrolled, we considered BMI (kg/m^2) and waist circumference (WC) measured on the morning of OGTT. We measured total cholesterol (TC) and HDL-C, using enzymatic procedures, apoB and apoA-I, using immunoturbidimetric assay, and TG using a colorimetric assay. All these assays were performed by a central laboratory with an ADVIA 1650/2400 Chemistry System. The glycaemia was determined by glucose oxidase, and insulin concentrations with an immunometric ''sandwich'' assay (Immulite 2000). As index of insulin resistance, we used the homeostatic model assessment (HOMA), based on fasting values of glucose and insulin, which has recently been updated in a computer model (HOMA2) recalibrated in line with current insulin assays [17]. The computer model, available from www.OCDEM.ox.ac.uk, gives values for insulin sensitivity expressed as HOMA2%S: the lower is HOMA2%S the higher is insulin resistance or the lower is insulin sensitivity [17].

To determine CV risk, in each subject we calculated the apoB/apoA-I ratio, the LDL-C with the Friedwald's formula: LDL-C = TC − HDL-C − TG/5, and also the non-HDL-C (TC minus HDL-C) recommended by the NCEP ATP III when TG levels are elevated [11]. Considering the conventional cut-off LDL-C values (100–130–160 mg/dL) [10] and the proposed cut-off apoB/apoA-I ratios to define a higher CV risk (0.9 for males and 0.8 for females) [8], we conceived a ''4 × 2'' table to create 4 groups, each composed of subjects with the same range of LDL-C. Within each LDL-C range group we compared subjects with different apoB/apoA-I ratio cut-off values. We also investigated, in all cohort considered, the presence of correlations between LDL-C and the apoB/apoA-I ratio, with components of MetS such as BMI, WC, OGTT data and HOMA2%S.