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Metabolism Clinical and Experimental 54 (2005) 1442–1447

Metabolism
Clinical and Experimental

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Fasting apoprotein B-48 level and coronary artery disease in a population without frank fasting hypertriglyceridemia

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Received 16 November 2004; accepted 21 May 2005

Abstract

The aim of this study was to test the hypothesis that fasting apoprotein B-48 level might be a surrogate marker of postprandial lipemia in evaluating the risk of coronary artery disease (CAD) in a population without frank abnormality in fasting lipid profile. One hundred twenty-three patients tested by coronary angiography were selected on the criteria of absence of treatment with hypolipidemic drugs, obvious hypertriglyceridemia (>2.85 mmol/L), or other conditions that may interfere with lipoprotein metabolism except diabetes. CAD was defined by more than 50% narrowing of vessel lumen, and its severity is determined by the number of arteries involved. Fasting apoprotein B-48 was measured by a competitive enzyme-linked immunosorbent assay method. There was no difference in fasting apoprotein B-48 levels between the groups with and without CAD (0.123 ± 0.096 vs 0.136 ± 0.125 μg/mL, respectively), whatever the sex or whether with or without diabetes. The apoprotein B-48 level was not related to the presence or the severity of CAD. There was also no correlation between fasting apoprotein B-48 levels and age, sex, body mass index, and usual fasting lipid parameters in both patients with and without angiographically proven CAD. Finally, among the features of metabolic syndrome, apoprotein B-48 was correlated with fasting triglyceride levels (r = 0.357, P < .01) only. In conclusion, the present study shows that in the absence of any major fasting abnormality in plasma lipid parameters, fasting apoprotein B-48 level, which has been associated with postprandial hyperlipidemia, does not predict the risk of CAD.

1. Introduction

Diabetes, hypertension, and tobacco use are well-identified cardiovascular risk factors. Among lipid parameters, low-density lipoprotein cholesterol (LDL-C) is considered as a main risk factor for atherosclerosis in both healthy and diabetic subjects, but the cardiovascular risk is still present for low values of LDL-C [1]. Indeed, the different trials for primary or secondary prevention of coronary artery disease (CAD) with statins reduced the cardiovascular morbidity and/or mortality by 20% to 40% only.

In fact, the major abnormalities seen in high-risk populations such as type 2 diabetic patients or subjects with metabolic syndrome are represented by a reduction in high-density lipoprotein cholesterol (HDL-C) [2,3] and an increase of triglycerides. The role of hypertriglyceridemia was more controversial, probably because of the heterogeneity of triglyceride-rich lipoproteins (TRLs) and the negative correlation found between triglycerides and HDL-C [4]. Nevertheless, in a meta-analysis, triglycerides were shown to be a risk factor for cardiovascular disease independent of HDL-C for both men and women in the general population [5].

Postprandial hyperlipidemia has also been considered to be an independent determinant of CAD risk (reviewed in Reference [6]). In this respect, intestinally derived TRLs could play an important role in both nondiabetic [7-11] and diabetic individuals [12,13]. In human beings, apoprotein B-48 is a specific marker of these intestinally derived TRLs (chylomicrons). Apoprotein B-48 receptor on macrophages,

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0026-0495/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2005.05.008

which specifically binds these particles, may participate in the constitution of foam cells in atherosclerotic plaques [14]. Apoprotein B-48 possesses also an unmasked proteoglycan binding site [15] susceptible to interact with artery wall proteoglycans. Intestinally derived, remnant-like particles were also shown to be associated with atherogenic, small, dense LDL profile [16]. In addition, abnormal clearance of these intestinally derived TRLs has also been described in metabolic situations at high risk for atherogenesis such as metabolic syndrome [17,18], diabetes [12], and end-stage kidney disease [19].

However, lipid tolerance tests dedicated to the evaluation of postprandial TRLs accumulation are of limited use in clinical practice. This lack of routine use is because of both practical difficulties linked to duration (6-8 hours), standardization, and absence of consensus on both the indication and the interpretation of data. In addition, relevant new information can be derived from this provocative test in individuals with normal or subnormal fasting triglyceride levels only because it has largely been demonstrated that postprandial hyperlipidemia is permanently altered in patients with frank fasting hypertriglyceridemia [20].

It was thus tempting to look for a surrogate marker of this test, which could easily be performed routinely on a unique blood sample. The fasting plasma apoprotein B-48 measurement could be such a surrogate, representing a residual marker of the efficiency of intestinally derived TRL clearance. Indeed, a correlation between this fasting parameter and the area under the curve of apoprotein B-48 values after oral fat test has been reported in 2 studies [18,21]. The increase of fasting apoprotein B-48 or remnant lipoproteins in patients with CAD remains debated [10-12,22]. To test the suitability and the reliability of this approach, we aimed to determine the fasting plasma apoprotein B-48 level in a series of subjects submitted to coronary angiography and to check whether this marker is associated with either the presence or the severity of coronary stenosis.

2. Patients and methods

2.1. Patients

This case-control study involved an adult population referred to the cardiology unit for coronary angiography. Patients submitted to this investigation were recruited except those with the following exclusion criteria: acute clinical event during the last 6 weeks (unstable angina, myocardial infarction, stroke, or cardiac insufficiency), untreated hypothyroidism, kidney failure (defined by plasma creatinine >200 μmol/L), hepatic cytolysis (AST and ALT >3 times the normal values), presence of ketone bodies in diabetic patients, and pregnancy. In addition, the patients usually treated with any class of hypolipidemic agent were excluded because both statins and fibrates are known to alter the clearance of intestinally derived TRLs [23]. Patients with overt hypertriglyceridemia (>2.85 mmol/L) were also excluded from the study because the measurement of apoprotein B-48 could be not entirely reliable [24]. As used in other similar studies [7,12], a documented coronary artery lesion was defined by a reduction of at least 50% of the arterial lumen assessed blindly on the angiogram by 2 different cardiologists. For the analysis, we evaluated the severity of CAD by the number of arteries involved.

Every recruited patient signed an informed consent form, and the design of the study received the agreement of the local ethics committee (CCPPRB Marseille 2). Using these criteria, 123 patients were included in the study: 69 patients (55 men and 14 women) with angiographically documented coronary artery lesions and 54 patients (30 men and 24 women) with absence of significant lesions.

The following clinical and biological parameters have been determined: age, sex, obesity (body mass index [BMI] = weight [kg]/height^2 [m^2]), waist girth, tobacco use, blood pressure, diabetes, plasma glucose, total cholesterol, HDL-C, LDL-C, triglycerides, thyrotropin, AST, ALT, plasma creatinine, insulinemia, and apoprotein B-48.

Hypertension was diagnosed if hypertensive treatment was started by a family physician or if the mean of 3 readings was above 140/90 mm Hg and increased blood pressure was confirmed during the next 2 weeks.

2.2. Lipids analyses

A sample of blood (10 mL) was drawn from the cubital vein after an overnight fast (12-15 hours), and plasma was collected after centrifugation. Total cholesterol, HDL-C, and triglycerides were quantitatively determined with commercially enzymatic test (CHOD-PAP, HDL-C plus, and GPO-PAP, respectively, Roche, Grenoble, France). The LDL-C was determined according to Friedewald's formula.

2.3. Apoprotein analyses

Apoprotein B-48 was determined with a competitive enzyme-linked immunosorbent assay method as previously described [24]. Briefly, a microtiter plate was coated with a C-terminal apoprotein B-48–specific heptapeptide. Plasma samples were incubated in presence of the mild detergent Triton X-100 to allow an efficient competition between immobilized antigen and plasma apoprotein B-48. There was no cross-reaction with apoprotein B-100. Intra-assay and interassay CVs were 5.4% and 5.5%, respectively.

2.4. Other biochemical determinations

Plasma glucose was determined with enzymatic test (Glucose/HK, Roche). ALT, AST, and plasma creatinine were determined with photometric assay (optimized Roche and Jaffe's method, respectively, Roche). Plasma thyrotropin and insulin levels were determined using an immunologic method (Elecsys System, Roche).

The QUICKI index was determined by the logarithmic transformation: 1/(log plasma insulin [μU/mL] + log plasma glucose [mg/dL]) as described by Katz et al [25].

Table 1
Clinical and biological characteristics of patients with or without angiographically documented CAD

	Whole population		Men		Women	
	CAD-free patients (n = 54)	Patients with CAD (n = 69)	CAD-free patients (n = 30)	Patients with CAD (n = 55)	CAD-free patients (n = 24)	Patients with CAD (n = 14)
Men/women	30/24	55/14**				
Age (y)	59 (12)	67 (13)**	58 (13)	66 (13)**	59 (13)	70 (12)*
BMI (kg/m^2)	28.5 (6)	25.2 (3.7)**	28.6 (5.6)	25.5 (3.7)**	28.5 (6.5)	24.2 (3.8)*
Waist girth (cm)	96 (15)	90 (10)	96 (14)	91 (10)	96 (16)	88 (11)
Tobacco use	21	42*	16	38	5	4
High blood pressure	25	29	12	23	13	6
Total cholesterol (mmol/L)	5.08 (1.03)	5.13 (1.11)	4.88 (1.03)	5 (1.08)	5.37 (0.8)	5.62 (1.11)
HDL-C (mmol/L)	1.16 (0.36)	1.21 (0.44)	1.08 (0.39)	1.19 (0.46)	1.24 (0.34)	1.34 (0.36)
LDL-C (mmol/L)	3.33 (0.88)	3.31 (0.85)	3.15 (0.95)	3.23 (0.85)	3.56 (0.72)	3.66 (0.83)
Triglycerides (mmol/L)	1.32 (0.54)	1.32 (0.52)	1.37 (0.55)	1.31 (0.54)	1.27 (0.52)	1.36 (0.54)
Apoprotein B-48 (μg/mL)	0.136 (0.125)	0.123 (0.096)	0.128 (0.137)	0.119 (0.101)	0.146 (0.11)	0.142 (0.076)
Diabetic patients	18	27	9	23	9	4
Glucose (mmol/L)	5.77 (2.78)	5.88 (2.39)	5.99 (3.33)	5.83 (2.39)	5.55 (2.11)	6.11 (2.28)
Insulin (mIU/L)	8.2 (6.6)	8.5 (7.3)	7.6 (4.6)	8.4 (7.9)	9 (9)	8.7 (5.1)
QUICKI index	0.37 (0.04)	0.37 (0.06)	0.37 (0.03)	0.38 (0.06)	0.37 (0.04)	0.36 (0.05)

Values are expressed as number or mean (SD). Mean (SD) values of insulin and QUICKI index are calculated in nondiabetic patients.
* $P < .05$.
** $P < .01$.

2.5. Statistical methods

Results are presented as mean (SD). Correlations were determined using Pearson test. Mann-Whitney U test was used to compare sets of data except for the sex ratio, the number of smokers, the number of diabetic patients, and the number of patients with high blood pressure, for which χ^2 test was used.

3. Results

The characteristics of the population studied are presented in Table 1. It is worthy to note that the plasma lipid profile of the whole population in terms of total cholesterol, LDL-C, and mean total cholesterol and triglycerides was in the normal range, confirming that our drastic selection criteria (patients without hypolipidemic drugs, triglyceride level *2.85 mmol/L) had excluded patients with known and/or treated hyperlipidemia. The CAD group also showed an apparent normal fasting lipid profile (mean total cholesterol, 5.13 mmol/L; mean HDL-C, 1.21 mmol/L; mean LDL-C, 3.31 mmol/L; mean triglycerides, 1.32 mmol/L) not statistically different from the group without CAD (mean total cholesterol, 5.08 mmol/L; mean HDL-C, 1.16 mmol/L; mean LDL-C, 3.33 mmol/L; mean triglycerides, 1.32 mmol/L) (Table 1). The groups with or without CAD are not different in this respect whatever the sex (Table 1).

There were only a few significant differences between the 2 groups: the group with CAD contained more men and

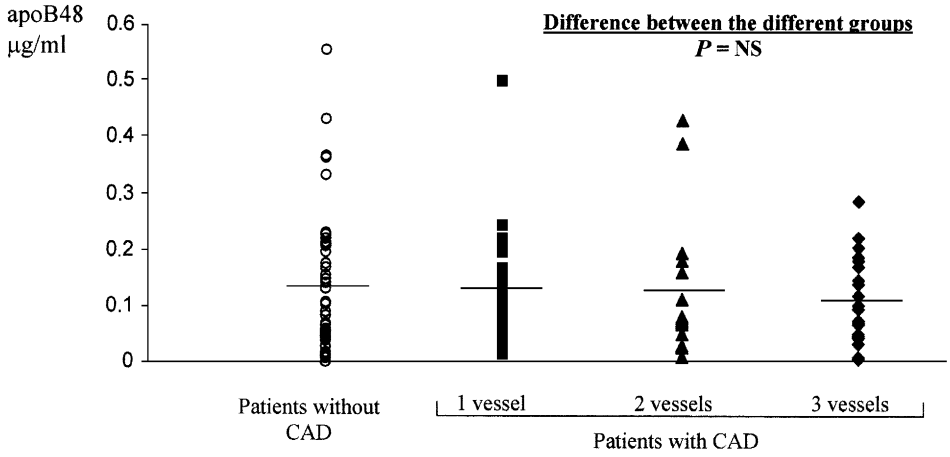

Fig. 1. Fasting apoprotein B-48 values according to the severity of CAD evaluated as the number of vessel with significant stenosis: monotroncular (1 vessel), bitroncular (2 vessels), or tritroncular (3 vessels). Mean value of each group is represented by a horizontal line. The difference between the groups is not statistically significant (P = NS).

smokers and was older and leaner than the group without CAD (Table 1).

In the male population, the men with CAD were older and leaner than the men without CAD, but their fasting lipid profile was not different (Table 1). In the female population, the women with CAD were older and leaner than women without CAD, but their fasting lipid profile was not different too (Table 1).

In the whole population as in each sex examined separately, fasting plasma apoprotein B-48 levels were unable to distinguish subjects with or without CAD. As shown in Fig. 1, the fasting apoprotein B-48 level showed a large interindividual variation and was not related to the severity of CAD as evaluated as the number of coronary arteries with significant stenosis (monotroncular, bitroncular, or tritroncular significant lesions).

Moreover, fasting apoprotein B-48 levels were not different between the diabetic and the nondiabetic groups (0.110 ± 0.081 vs 0.140 ± 0.122 μg/mL, respectively, P = NS) and between diabetic patients with and without CAD (0.104 ± 0.070 vs 0.119 ± 0.096 μg/mL, respectively, P = NS).

We also looked for association of fasting apoprotein B-48 with classic features of metabolic syndrome in the whole population. In this study, 18 women (5 with CAD and 13 without CAD) and 22 men (15 with CAD and 7 without CAD) had a metabolic syndrome as defined by the National Cholesterol Education Program Adult Treatment Panel III [26]. Fasting apoprotein B-48 values were not different between the patients with and without metabolic syndrome (0.134 ± 0.108 vs 0.127 ± 0.110 μg/mL, respectively, P = NS). A positive correlation was found between fasting triglyceride values and fasting apoprotein B-48 values (Fig. 2), but not between fasting apoprotein B-48 values and other markers of metabolic syndrome such as waist girth (data not show), fasting plasma insulin levels (measured in nondiabetic patients; data not shown), QUICKI index (calculated in nondiabetic patients; data not shown), HDL-C (data not shown), fasting plasma glucose level (measured in nondiabetic patients; data not shown), and LDL-C (data not shown) or BMI (data not shown).

Finally, when considering the 26 patients with a fasting apoprotein B-48 value of 0.2 μg/mL or higher, we did not find any specific characteristics in this population (data not shown).

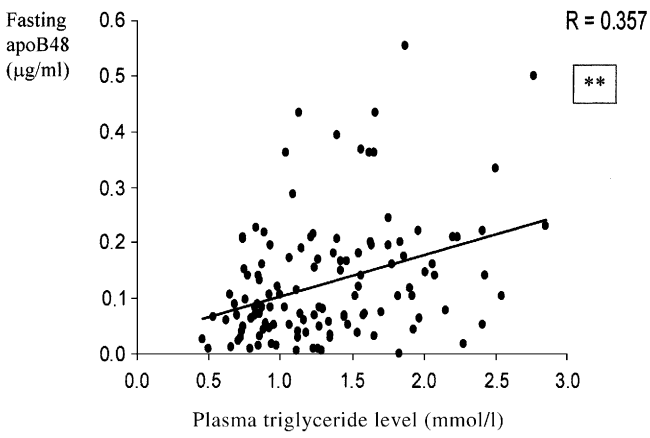

Fig. 2. Correlations between fasting apoprotein B-48 and fasting triglyceridemia. $^{**}P < .01$.

4. Discussion

This study, which was designed to determine whether fasting apoprotein B-48 level, representative of the residual presence of intestinally derived TRLs, could be a marker of cardiovascular risk in a population without obvious abnormality of relevant fasting lipid parameters, failed.

These striking results deserve several comments. The initial hypothesis of a pathogenic link of CAD with a defect in clearance of exogenous TRLs was supported by several converging arguments from theoretical and experimental points of view. First, apoprotein B-48 participates in the adhesion of such lipoproteins to vascular proteoglycans [15] and their capture by macrophages after binding to an apoprotein B-48–specific receptor [14]. Secondly, in some murine models of accelerated atherogenesis such as invalidation of apoprotein E or overexpression of apoprotein C-III genes in mice, a drastic increase of apoprotein B-48–containing TRLs was observed [27,28]. In human atherosclerotic plaques, the level of apoprotein B-48 relative to apoprotein B-100 was found to be much greater than would be expected based on the relative plasma concentrations [29]. In contrast, the attempts to correlate the plasma level of intestinally derived lipoproteins with angiographically proven CAD are rather controversial. In some studies, markers of intestinally derived TRLs as such particles as either apoprotein B-48/apoprotein B-100 ratio in Sf > 60 lipoparticles [7] were found to be increased after fat load in patients with CAD in comparison to controls. Meyer et al [10] observed that apoprotein B-48 concentration in $d < 1.006$ mg/dL fraction in both fasting and posttest meal situations was increased in 12 normocholesterolemic and normotriglyceridemic women with angiographically proven CAD. In contrast, Orth et al [30] and Schaefer et al [31] did not observe any difference in intestinally derived TRLs after a fat load in a CAD population. However, Schaefer et al [31] reported an increase in remnant-like particle triglyceride or cholesterol levels at fasting in the CAD group. Finally, in a population of subjects at risk for early development of CAD selected on familial history of CAD, Slyper et al [32] did not observe any alteration of exogenous TRL clearance. These discrepancies from one study to another one might be attributed to the heterogeneity in the parameters representative of clearance of exogenous TRLs and the selected populations.

Indeed, the present negative results can be explained by the biased selection of the patients excluding both hypercholesterolemic subjects already treated by statins and individuals with frank hypertriglyceridemia. One can assume that at least one part of the CAD risk associated

with impaired clearance of exogenous TRLs can be secondary to other abnormalities such as hypertriglyceridemia due to hyperVLDLemia and/or hypoHDLemia. Indeed, a positive correlation was found between apoprotein B-48 and triglycerides levels at fasting in the present study as in others [21]. In fact, normalization of hypertriglyceridemia by hypolipidemic drugs drastically reduced apoprotein B-48 levels in both fasting and postprandial conditions [33]. It is obvious that in the presence of high levels of endogenous TRLs, the clearance of intestinally derived TRLs is impaired, likely because both particles compete in the clearing processes (reviewed in Reference [30]). In most of the studies relating CAD to excess of exogenous TRLs, except one (reviewed in Reference [34]), the range of fasting triglyceridemia was rather large.

Note that angiographic evaluation of CAD is based on the measurement of the vessel lumen only. The cut point of 50% stenosis is arbitrary, and there is a possibility of some overlap between groups. In addition, necropsic and intravascular sonography examinations have shown that the arterial wall remodeling permits accumulation of atherosclerotic burden before there is any detectable narrowing of the vessel lumen (reviewed in Reference [35]). It is thus likely that angiographic examination could lessen the severity of CAD and might be unable to detect for any mild relationship between fasting apoprotein B-48 level and the development of CAD. This possible overlap between the groups mainly due to the drastic selection of the patients and the underestimation of CAD lesions can explain that none of the classic markers of cardiovascular risk are different between the groups.

Another unexpected finding observed in the present study was the absence of any association between fasting apoprotein B-48 level and various markers of the metabolic syndrome and/or insulin resistance except triglycerides. Nevertheless, postprandial intestinally derived TRL clearance has been found impaired in obese subjects with features of the metabolic syndrome [17,18]. In addition, production of TRL-containing apoprotein B-48 by enterocytes has been shown to be increased in both postprandial and fasting conditions in animal models of insulin resistance [36,37]. The observed discrepancy between some literature data and the present results is likely because of the heterogeneity of TRLs and the low level of residual intestinally derived lipoproteins after overnight fasting. Indeed, TRLs represent a mixture of endogenous and exogenous lipoproteins. Most of these particles, even during the postmeal period, are represented by very low-density lipoprotein (VLDL) (reviewed in Reference [6]). It is considered that approximately 50% to 80% of the TRL increment during this period is accounted for by the VLDL compartment, mostly large VLDL 1 in insulin-resistant state (reviewed in Reference [34]). In the fasting state, it is obvious that the ratio in pool sizes between apoprotein B-100 and apoprotein B-48 is even higher. It is thus possible that the variation of residual apoprotein B-48 levels after overnight fasting could be not sensitive enough to reflect the influence of insulin-resistant state on intestinally derived TRL metabolism, particularly in a population without frank fasting hypertriglyceridemia.

In conclusion, the present study shows that in the absence of major fasting abnormality in plasma lipid parameters (total cholesterol, LDL-C and HDL-C, and triglycerides), the measurement of fasting apoprotein B-48 is unable to detect the risk of CAD, which has been associated with postprandial hyperlipidemia.

Acknowledgment

We are thankful to Chantal Bertorello from the Département d'Informatique Médicale, Hôpital Sainte Marguerite, for her statistical assistance. We also thank Prof Bruno Verges and Dr Lee Leserman for their helpful comments.

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