It has been amply documented in several large studies [1,2] that serum apolipoprotein (apo) B or the apo B/A-I ratio is a good predictor of cardiovascular disease, a more reliable one than LDL- or nonHDL-cholesterol [3]. Levels of apo B correlated significantly with insulin sensitivity and LDL size (but not with LDL-cholesterol levels) in the multi-ethnic Insulin Resistance Atherosclerosis Study [4]. The association of apo B with diabetes and metabolic syndrome (MetS) has been shown, as has its potential role as a subclinical inflammatory agent [5]. However, the issue whether or not apo B is of additive value to obesity and C-reactive protein (CRP) as a conventional marker of inflammation in the prediction of MetS and/or diabetes has thus far not been explored and identified.

We, therefore, investigated the determinants of apo B as well as the role of apo B in predicting diabetes, MetS and some of its components (hypertension and dyslipidemia) in the cohort of the Turkish Adult Risk Factor study which is representative of Turkish middle-aged and elderly women, among whom MetS is highly prevalent [6]. The former is an ongoing longitudinal survey carried out periodically since 1990 in seven geographical regions of Turkey, representatively stratified for sex, age, geographical, and rural-urban distribution [7]. The mentioned study was carried out prospectively in 2,348 participants [8]. Individuals with diabetes were diagnosed with criteria of the American Diabetes Association, namely when plasma fasting glucose was ≥ 126 mg/dl (or 2-hour postprandial glucose > 200 mg/dl) and/or the current use of diabetes medication. Individuals with MetS were identified when 3 out of the 5 criteria of the National Cholesterol Education Program (ATP III) were met, modified for male abdominal obesity (≥ 95 cm). Atherogenic dyslipidemia (or simply dyslipidemia) referred to combined presence of high triglyceride (≥ 150 mg/dl) and low HDL-cholesterol (< 40/< 50 mg/dl) values as defined by the ATP III. Hypertension was defined as a blood pressure of ≥ 140 mmHg and/or ≥ 90 mmHg, and/or use of antihypertensive medication. Concentrations of serum apo B and CRP were measured by the Behring nephelometry. Because of the skewed distribution of concentrations of insulin and CRP, these were log-transformed for all calculations. Three tertiles of apo B values were formed demarcated by cutpoints of 95 and 120 mg/dl.

At baseline examination, mean age of participants was 48.3 ± 12 years, and mean follow-up constituted 5.9 years (total 11,900 person-years). The study sample is characterized by a high gross incidence (4.7% per annum) of MS and by apo B levels that were on average only 6 mg/dl lower than LDL-cholesterol, a constellation which suggests a relatively high proportion of small, dense LDL particles [9] prevailed in this cohort.

Determinants at baseline of final apo B values were sought by linear regression analysis in a model comprising sex, age, LDL-cholesterol, triglycerides, HOMA index, waist circumference, and systolic BP. LDL-cholesterol, followed by triglycerides contributed to 29% of variance in both sexes combined, while the remaining parameters did not prove significant.
After exclusion of individuals with the individual metabolic disorders at baseline, prediction of each disorder by apo B tertiles was analyzed in two separate logistic regression models: adjusted only for age and waist circumference, or for age, waist circumference, C-reactive protein (CRP), physical activity grade, household monthly income, and menopause. The top versus bottom apo B tertile predicted significantly newly developing MetS in both sexes separately with 2-fold RRs (p < 0.02) and the development of high triglyceride/low HDL-cholesterol dyslipidemia with nearly 3-fold RRs (p = 0.001), in the fully adjusted model (bars on right, Figure 1).

Development of hypertension was predicted only in women by the apo B top tertile (fully adjusted RR 1.71 [95%CI 1.001; 2.92]), while the significance of the prediction regarding age-adjusted diabetes in women (RR 1.86 [95%CI 1.04; 3.36]) attenuated somewhat after adjustment for the stated confounding factors.

These observations indicate that serum apo B (as a marker of small, dense LDL particles) strongly determines the development of atherogenic dyslipidemia in both sexes among Turks and, thereby, also that of MetS, and as a novelty, these processes seem to have components independent of central adiposity and low-grade inflammation. The studied process appears not to be involved in regard to hypertension and type-2 diabetes among Turkish men, while it has a modest but significant contribution in women. The gender difference may be related to the assumed fact that (hypertriglyceridemia with) elevated apo B in Turkish women is significantly affected by low sex hormone-binding globulin (SHBG), independent of central obesity and insulin resistance [10], and behaves fully in concert with the balance between CRP and adiponectin levels but not fully with serum triglycerides. In men, apo B is not independently affected by SHBG, thus apo B and serum triglycerides seem to be tightly interrelated. Additionally, there is evidence that fibrinogen and adiponectin levels each comprise a component independent of central adiposity and insulin resistance in men.

In the current study, the predictive capacity of apo B for combined cardiometabolic disorders might be ascribed to the close relationship of apo B with subclinical inflammation. CRP had little contribution to the prediction of cardiometabolic risk (a doubling of value corresponded to ~5% to 9% increment in RR) independent of waist circumference and apo B, while apo B supplied substantial predictive information added to waist circumference and CRP. Apo B is a good surrogate measure of increased LDL particle numbers in people with MetS and insulin resistance [4], and small LDL particle number was best correlated with apo B (and triglycerides and HDL-cholesterol) in the Framingham Heart study [11]. To what extent these findings apply to populations with a lower prevalence of MetS remains to be seen.

We conclude that apo B concentrations which reflect the number of small, dense LDL particles in plasma are a significant predictor of cardiometabolic risk among adults with a high prevalence of MetS, independent of waist circumference and CRP.

References


Figure 1. Each pair of bars denotes mean relative risk (and 95% CI) across the upper and lower apo B tertiles (> 120 vs < 95 mg/dl) of the subsequent development of the respective cardiometabolic disorder in men and women. Bars on left indicate values adjusted for age and waist circumference, bars on right additionally for CRP, physical activity grade, and family income (and menopause).