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ORIGINAL ARTICLE

Serum apolipoprotein B predicts dyslipidemia, metabolic syndrome and, in women, hypertension and diabetes, independent of markers of central obesity and inflammation

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Objectives: To investigate the role of serum apolipoprotein (apo) B levels in predicting metabolic syndrome (MS), hypertension, atherogenic dyslipidemia and type II diabetes.
Methods: Prospective evaluation of 1125 men and 1223 women, aged 28–74 years, participating in the survey 1997/1998 who had serum apo B determinations and were followed-up for a mean 5.9 years. Tertiles of apo B were formed by cut points by 120 and 95 mg/dl. MS was defined by modified ATPIII criteria.
Results: Apo B values exhibited no significant difference among sexes. Low-density lipoprotein (LDL)-cholesterol and triglycerides were their leading determinants on linear regression analysis. By logistic regression analyses, the top versus bottom apo B tertile predicted significantly newly developing MS in both sexes separately with two-fold relative risks (RRs) ($P<0.02$) and the development of high triglyceride/low high-density lipoprotein-cholesterol dyslipidemia with nearly threefold RRs ($P=0.001$), after adjustment for waist circumference, C-reactive protein (CRP), physical activity grade and family income category. 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 after adjustment for the stated confounding factors.
Conclusions: 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 MS, independent of waist circumference and CRP.
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Introduction

Plasma apolipoprotein (apo) B has recently been closely associated with metabolic syndrome (MS). Apo B(100) levels in 298 persons with diabetes demonstrated an association with MS, and body mass index (BMI) was accounted for a great part of power of this relationship.[1] Levels of apo B correlated significantly with insulin sensitivity and low-density lipoprotein (LDL) size (but not with LDL-cholesterol levels) in the multiethnic Insulin Resistance Atherosclerosis Study.[2] Among over 7000 persons participating in the NHANES survey, MS was associated with high apo B (odds ratio 2.97) and higher homeostatic model assessment index (HOMA) insulin resistance (IR), after adjustment for age, sex, BMI and other confounders.[3] One-quarter of 2103 subjects who had high apo B levels than would have been predicted based on their LDL-cholesterol concentrations, were more obese and manifested several features of MS, and concomitantly had increased cardiovascular risk.[4] It was also shown that apo B was more closely associated than nonhigh-density lipoprotein (HDL)-cholesterol with central obesity, IR and inflammation,[5] and authors thus suggested that apo B is a

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better risk parameter than nonHDL-cholesterol for identifying a subgroup of individuals with or without MS with elevated cardiovascular risk.

Investigating the predictors of inflammatory markers (IL-6, C-reactive protein (CRP), tumor necrosis factor (TNF)-α and others) in 77 nondiabetic postmenopausal overweight and obese women, apo B was found to be the primary predictor among a variety of risk parameters (adiposity, blood pressure (BP), IR, triglycerides, apo B/A-I ratio, Framingham risk points, etc).[6] It was suggested that high apo B would be associated with elevated risk of developing coronary heart disease ((CHD) and) diabetes. Seeking differences among sexes in the association of apo B and other risk factors with the MS, Dallongeville *et al*.[7] reported that the contribution of apo B to MS was significantly less in women than in men and suggested that different criteria are necessary to define the MS in women and men. In cross-sectional studies among middle-aged Swedish men, a high apo B/A-I ratio was also found to be associated with MS or the number of its components.[8,9]

Despite this knowledge on the association of apo B with diabetes and MS and on its potential role as a subclinical inflammatory agent, the issue whether or not apo B is (independently) predictive of MS and/or diabetes has not been explored and identified so far. It is, therefore, the purpose of the present prospective study to investigate the determinants of apo B as well as the role of apo B in predicting diabetes, MS and some of its components (hypertension and dyslipidemia) in a cohort, which is representative of Turkish middle-aged and elderly women, among whom MS is highly prevalent.[10]

Population and methods

Population sample

The *Turkish Adult Risk Factor Study* is a prospective survey on the prevalence of cardiac disease and risk factors in adults in Turkey carried out periodically almost biennially since 1990 in 59 communities scattered throughout all geographical regions of the country.[11] It involves a random sample of the Turkish adult population, representatively stratified for sex, age, geographical regions and for rural–urban distribution.[11] As combined measurements of waist circumference, HDL-cholesterol and apo B were first performed at the follow-up visit in 1997/1998, the latter examination formed the baseline. Participants were 28 years of age or older at baseline examination. Of the survivors, 8% were examined up to the survey 2001/2002, 14% up to 2003, the remainder having been examined lastly in the survey 2004/2005. Serum apo B was measured in 2448 men and women. Individuals aged >74 years and six persons having CRP values >100 mg/l, very extreme values usually not associated with cardiometabolic disorders, were excluded. This limited the study sample to 2348 adults (1125 men and 1223 women). Over 90% of baseline participants of the present and the previously reported prospective study[10] overlapped. The survey conformed to the principles embodied in the Declaration of Helsinki and was approved by the Istanbul University Ethics Committee. Individuals of the cohort were visited in their addresses on the eve of the examination and were requested to give written consent for participation after having read an explanatory note, which manifested by their voluntary participation the next morning. Data were obtained by history of the past years via a questionnaire, physical examination of the cardiovascular system, sampling of blood and recording of a resting electrocardiogram.

Measurements of risk variables

Blood pressure was measured in the sitting position on the right arm, and the mean of two recordings at least 3 min apart was recorded. Weight was measured without shoes in light indoor clothes using a scale. Waist circumference was measured with a tape (Roche LI95 63B 00), the subject standing and wearing only underwear, at the level midway between the lower rib margin and the iliac crest. BMI was calculated as weight divided by height squared (kg/m^2). Physical activity was graded by the participant himself into four categories of increasing order with the aid of a scheme.[11] Reported family income was categorized increasingly into four nearly equal groups.

Plasma concentrations of cholesterol, fasting triglycerides, HDL-cholesterol and glucose were determined at baseline examination by the enzymatic dry chemistry method using a Reflotron apparatus. LDL-cholesterol values were computed according to the Friedewald formula. In the final three surveys, the stated parameters, as well as apo B, insulin and CRP values were assayed in a single central laboratory. Blood samples collected into dry vacutainers were spun at 1000 *g* for 10 min and sera shipped within a few hours on cooled gel packs at 2–5°C to Istanbul to be stored in deep freeze at -75°C, until analyzed at a central laboratory in the same city. Concentrations of insulin were determined by the chemiluminescent immunometric method using Roche kits and Elecsys 1010 immunautoanalyzer (Roche Diagnostics, Mannheim, Germany). Concentrations of serum apo B and CRP were measured by the Behring nephelometry, the latter using an N Latex CRP mono reagent (Behring Diagnostics, Marburg, Germany). Within run and day to day coefficients of variation for apo B were 2.3 and 4.1%, and for CRP were 1.3 and 2.9%, respectively. External quality control was performed with a reference laboratory in a random selection of 5–6% of participants. Data on CRP and insulin were available from the survey 2000/2001 on in nearly 90 and 50% of participants, respectively, and tests were made again in 2004/2005. Insulin resistance was assessed from fasting insulin and glucose concentrations with the HOMA equation: HOMA = fasting glucose (mmol/l) $\times$ fasting insulin (μU/ml)/22.5.[12]

Definitions and outcomes

Individuals with diabetes were diagnosed with criteria of the American Diabetes Association,[13] namely when plasma fasting glucose was ⩾126 mg/dl (or 2-h postprandial glucose >200 mg/dl) and/or the current use of diabetes medication. Individuals with metabolic syndrome were identified when three out of the five criteria of the National Cholesterol Education Program (ATP III)[14] were met, modified for prediabetes (fasting glucose 100–125 mg/dl[15] and further for abdominal obesity using as cut point ⩾95 cm in men, as recently assessed in the Turkish Adult Risk Factor study.[16,17] 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 BP ⩾140 mm Hg and/or ⩾90 mm Hg, and/or use of antihypertensive medication. Missing data on triglycerides in one-eighth of the sample did not preclude the identification of MS because availability of no more than three criteria were required, and the MS and/or dyslipidemia status of the subsequent survey was adopted in few individuals presenting two positive criteria. Values of the baseline examination were used to evaluate prospective developments.

Data analysis

Three tertiles of apo B values were formed demarkated by cut points of 95 and 120 mg/dl. Following number of adults were comprised in tertiles I–III: 763, 687 and 898. As a result of the skewed distribution of concentrations of insulin and CRP, these were log-transformed for all calculations. Descriptive parameters were shown as mean±s.d. and in percentiles. Two-sided *t*-tests and Pearson's χ^2 tests were used to analyze the differences in means and proportions between groups. In the prediction of a dependent variable, the cohort in whom that particular variable existed at baseline examination was excluded from the multivariate analysis. Linear regression analysis was made for predictors of apo B in two models, the second one comprising fasting insulin because the latter might be expected to be an independent determinant. Estimates (and 95% confidence intervals (CI)) for relative risk (RR) of a dependent variable were obtained by use of logistic regression analyses in models that controlled for potential confounders. With the purpose of comparing more clearly the associated risk, hazard ratio (HR) estimates were obtained when needed for comparing the effect of multiple independent parameters. HR expresses the risk in terms of one s.d. of the given variable, for which was taken into account that the gradient across the apo B tertiles represented 1.79 s.d. (1 s.d. = 41.4 mg/dl). The RR of log-transformed independent variable was assessed in terms of doubling and calculated by multiplying the log of the RR value by 0.2 and then taking its antilog. A value of $P<0.05$ on the two-sided test was considered statistically significant. Statistical analyses were performed using SPSS-10 for Windows (SPSS Inc., Chicago, IL, USA Nr. 9026510).

Results

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). A significant sex difference in serum concentrations of apo B was lacking but apo B/apo A-I ratio was significantly different; the mean, median (interquartile range) values are presented in Table 1 separately. For comparison, baseline values for CRP and waist circumference are provided as well. In the interquartile range apo B values were lower than LDL-cholesterol by 2.5 and 9 mg/dl in men and women, respectively.

Determinants of apo B values at baseline

Table 2 provides results of a linear regression analysis for apo B levels at baseline in two models. The model comprising HOMA index, measured in fewer subjects ($n=962$), exhibited nonetheless a high significance (F= 4.7) and included covariates of 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, whereas the remaining parameters did not prove to be significant. In the model without HOMA index, and nonHDL-cholesterol replacing LDL-cholesterol and triglycerides, waist girth tended to be a borderline significant independent determinant of subsequent apo B levels, apart from nonHDL-cholesterol.

Table 1 Values of mean, median and interquartile range of apolipoprotein B and apo B/A-I ratio, C-reactive protein and waist circumference, by gender

	Men				*Women*			
	Apo B/A-ratio	*Apo B (mg/dl)*	*CRP (mg/l)*	*Waist (cm)*	*Apo B/A-ratio*	*Apo B (mg/dl)*	*CRP (mg/l)*	*Waist (cm)*
n	981	1125	980	1125	1035	1223	1082	1223
25 percentile	0.725	89.7	0.90	87	0.63	87.2	1.10	83
50 percentile	0.89	109.4	1.80	95	0.78	108.1	2.40	91
75 percentile	1.10	132	3.90	101	0.98	133	5.30	100
Mean	0.95±0.42	114.7±40.8	1.93±1.1	94.7	0.845±0.34	114.7±42	2.34±1.1	91.5

Abbreviations: APO, apolipoprotein; CRP, C-reactive protein. $P<0.001$ between means of apo B/A–I ratio among sexes.

Table 2 Determinants at baseline of subsequent apolipoprotein B in two models

	Model 1						*Model 2*			
	Adults, 2268		*Men, 1088*		*Women, 1180*		*Men, 409*		*Women, 553*	
	β *coeff*	P	β *coeff*	P	β *coeff*	P	β *coeff*	P	β *coeff*	P
Sex (F)	−0.44	NS								
Age (years)	0.07	NS	−0.35	NS	0.21	0.054	0.07	NS	0.07	NS
Waist circumference (cm)	0.124	0.07	0.07	NS	0.14	0.12	0.08	NS	0.11	NS
Systolic BP (mm Hg)	0.04	NS	0.08	0.17	0.01	NS	0.10	NS	0.04	NS
NonHDL-cholesterol (mg/dl)	**0.51**	0.000	**0.55**	0.000	**0.48**	0.000				
LDL-cholesterol (mg/dl)							**0.48**	0.000	**0.52**	0.000
Triglycerides (mg/dl)							**0.08**	0.000	**0.15**	0.000
HOMA index[a]							4.24	NS	−4.38	NS
	$F=165$, $P<0.001$		$F=101$, $P<0.001$		$F=107$, $P<0.001$		$F=24.8$, $P<0.001$		$F=40.9$, $P<0.001$	

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; HOMA, homeostatic model assessment index; LDL, low-density lipoprotein; NS, nonsignificant.
[a]Log-transformed. Bold values indicate significant values.

Prediction of new MS

Prediction of cardiometabolic disorders by apo B tertiles were analyzed in three logistic regression models: adjusted only for age (model 1), for age and waist circumference (model 2), for age, waist circumference, CRP, physical activity grade, household monthly income and menopause (model 3).

After exclusion of individuals of MS (45%) at baseline, 631 men and 651 women were analyzed for newly developing MS. In men (Table 3) and women (Table 4) tertiles II and III significantly predicted MS. For combined sexes the age adjusted RR in the mid-tertile was 1.72 (95% CI 1.26; 2.36) and for the top tertile 2.46 (95% CI 1.82; 3.33), corresponding to a HR 1.65. The top tertile retained significance in both genders with an RR 2.01, even after adjustment for the also significant waist circumference and CRP.

Prediction of new hypertension

Similarly, 1375 men and women were analyzed for hypertension, which newly developed in 267 adults. Compared with the bottom tertile, the top tertile significantly predicted hypertension after adjustment for waist circumference and log CRP (RR 1.55, $P=0.018$). Although apo B tertiles failed in men to predict significantly hypertension in all models, the top tertile in women did predict even in the fully adjusted model (RR of 1.71; 95% CI 1.001; 2.92) (Tables 3 and 4).

Prediction of new dyslipidemia

High triglyceride/low HDL-cholesterol dyslipidemia was the parameter most strongly predicted by apo B categories. Even the middle tertile predicted it significantly in both genders with RRs of nearly three in men and two in women, after full adjustment (Tables 3 and 4). The increments in RR in the top tertile were modest.

Prediction of new diabetes

As seen in Table 3, apo B tertiles were not predictive in men, even when adjusted for age alone, among whom waist circumference was a significant and important predictor. Among women, age-adjusted apo B proved to predict the development of diabetes with an RR 1.86 (95% CI 1.04; 3.36) but the significance was attenuated when waist circumference was added or full adjustment was made (Table 4).

Discussion

In a study sample representative of middle-aged and elderly Turkish men and women, new developments of dyslipidemia and MS over a follow-up of nearly 6 years, were each significantly predicted by age-adjusted tertiles of apo B levels in both genders, as were hypertension and diabetes in women. With the exception of diabetes, associations in the top tertiles remained significant after adjustment for waist circumference, CRP and certain lifestyle variables.

The study sample is characterized by a high prevalence (45%) and gross incidence (4.7% per annum) of MS and by apo B levels (114.7 mg/dl) 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[18] prevailed in this cohort. Despite considerably lower LDL-cholesterol values, the median apo B level of 109 mg/dl is comparable to that of other populations.[19] Insulin resistance, reported to be an independent predictor of apo B in normoglycaemic Koreans,[20] appeared to be a weaker independent determinant of apo B levels in our population sample.

Magnitude of associations

Serum concentrations of apo B significantly predicted virtually all the studied types of cardiometabolic disorders

Table 3 Tertiles of apo B, age-adjusted, in prediction of cardiometabolic disorders in men

Model	*1*		*2*		*3*[a]	
	RR	*95% CI*	*RR*	*95% CI*	*RR*	*95% CI*
Dependent variable: metabolic syndrome						
	$n=$(631, 179 new MS)		(631, 179 new MS)		(560, 164 new MS)	
II: 95–120 mg/dl	**1.73**	1.11; 2.70	1.48	0.92; 2.36	1.32	NS
III: >120 mg/dl	**2.55**	1.66; 3.93	**2.00**	1.26; 3.17	**1.81**	1.11; 2.97
Waist circumference (cm)			**1.089**	1.07; 1.011	**1.087**	1.06; 1.11
C-reactive protein[b]					1.30	0.85; 1.98
Dependent variable: diabetes						
	(1075, 84 new DM)		(1074, 84 new DM)		(932, 69 new DM)	
II: 95–120 mg/dl	1.18	NS	0.99	NS	0.76	NS
III: >120 mg/dl	1.12	NS	0.95	NS	0.86	NS
Waist circumference, cm			**1.057**	1.035; 1.08	**1.047**	1.023; 1.072
C-reactive protein[b]					0.95	NS
Dependent variable: hypertension						
	(733, 135 new HT)		(733, 135 new HT)		(641, 119 new HT)	
II: 95–120 mg/dl	1.26	NS	1.16	NS	1.03	NS
III: >120 mg/dl	1.48	0.93; 2.35	1.31	NS	1.33	NS
Waist circumference (cm)			**1.035**	1.02; 1.06	**1.034**	1.12; 1.056
C-reactive protein[b]					0.92	NS
Dependent variable: dyslipidemia						
	(495, 81 new DI)		(495, 81 new DI)		(457, 77 new DI)	
II: 95–120 mg/dl	**2.87**	1.50; 5.51	**2.81**	1.46; 5.4	**2.95**	1.48; 5.9
III: >120 mg/dl	**3.40**	1.78; 6.47	**3.31**	1.73; 6.35	**3.30**	1.65; 6.59
Waist circumference (cm)			1.007	NS	1.00	NS
C-reactive protein[b]					**2.29**	1.36; 3.87

Abbreviations: CI, confidence interval; DI, dyslipidemia; DM, diabetes mellitus; HT, hypertension; MS, metabolic syndrome; NS, nonsignificant; RR, relative risk. First number in brackets denote number of subjects in model, second number the number of newly developed cardiometabolic disorder in the follow-up. Cardiometabolic disorders at baseline excluded. Bottom tertile of apo B (<95 mg/dl) served as reference (=RR 1.0) in each model. [a]Also adjusted for physical activity grade and family income category, not significant for any dependent variable. [b]Log-transformed. Bold values indicate significant values.

that developed in this cohort. The strength of the associations was high in general, in as much as age adjusted HRs ranged from 1.42 to 1.46 relative to diabetes and hypertension (in women alone) to 1.78 relative to atherogenic dyslipidemia; for MS it emerged as 1.65. The threshold of prediction was low because the risks with respect to dyslipidemia and MS and, in women, to hypertension were significantly elevated already in the apo B middle tertile (95–120 mg/dl) suggesting a graded and fairly linear risk increment. Adjustment for markers of central obesity and low- grade systemic inflammation disclosed that the cardiometabolic risk involved with apo B concentrations was independent of these components.

The question whether significant associations between apo B and several cardiometabolic disorders are limited to populations with a relatively high prevalence of MS remains open. That this is not strictly the case is apparent from various cross- sectional studies,[1–5] outlined in the introduction, in which close associations between MS, insulin sensitivity, LDL size, markers of central obesity, inflammation on the one hand and levels of apo B on the other have been reported. With increasing number of ATP III criteria of MS and HOMA index, progressively higher concentrations of apo B were observed in normoglycemic Koreans.[20] Yet, as far as we could ascertain, prospective studies on prediction of these conditions by apo B were lacking, in contrast to the high number of papers that analyzed the predictive value of apo B in relation to CHD or cardiovascular disease.[8,21] The current study documents for the first time such predictive capability of apo B levels, not only for an isolated component of MS, but conjointly for atherogenic dyslipidemia, MS itself in the same cohort and, as concerns women, for hypertension and diabetes.

Sex divergence in the dynamics of cardiometabolic risk

In the prediction of the studied cardiometabolic disorders by apo B, dyslipidemia exhibited an association with the greatest strength. The documented predictive value of waist circumference was assumed by apo B in both genders. With respect to hypertension, apo B did predict its development in women but not in men, independent of markers of central obesity and proinflammatory state, which, despite the recognition of the relation between IR and hypertension, is a novel finding. This indicates that although the association of apo B with hypertension was

Table 4 Tertiles of apo B, age-adjusted, in prediction of cardiometabolic disorders in women

Model	*1*		*2*		*3*[a]	
	RR	*95% CI*	*RR*	*95% CI*	*RR*	*95% CI*
Dependent variable: metabolic syndrome						
	$n=$(651, 174 new MS)		(650, 174 new MS)		(583, 164 new MS)	
II: 95–120 mg/dl	**1.75**	1.12; 2.75	**1.67**	1.05; 2.66	**1.85**	1.12; 3.04
III: >120 mg/dl	**2.10**	1.36; 3.26	**2.09**	1.33; 3.29	**2.21**	1.34; 3.64
Waist circumference (cm)			**1.061**	1.04; 1.08	**1.064**	1.04; 1.086
C-reactive protein[b]					1.40	0.89; 2.18
Family income					*P* trend 0,043	
Dependent variable: diabetes						
	(1146, 84 new DM)		(1145, 84 new DM)		(1015, 75 new DM)	
II: 95–120 mg/dl	1.54	NS	1.45	NS	1.65	0.81; 3.34
III: >120 mg/dl	**1.86**	1.04; 3.36	1.60	0.88; 2.9	1.68	0.87; 3.26
Waist circumference, cm			**1.037**	1.017; 1.57	**1.031**	1.01; 1.054
C-reactive protein[b]					**2.18**	1.24; 3.81
Physical activity grade					**0.70**	0.48; 1.006
Dependent variable: hypertension						
	(642, 132 new HT)		(642, 132 new HT)		(588, 125 new HT)	
II: 95–120 mg/dl	**1.69**	1.01; 2.84	1.59	0.94; 2.69	1.51	0.87; 2.62
III: >120 mg/dl	**2.04**	1.24; 3.36	**1.87**	1.13; 3.11	**1.71**	1.001; 2.92
Waist circumference, cm			**1.041**	1.02; 1.06	**1.038**	1.018; 1.058
C-reactive protein[b]					1.25	NS
Dependent variable: dyslipidemia						
	(657, 127 new DI)		(657, 127 new DI)		(618, 122 new DI)	
II: 95–120 mg/dl	**1.97**	1.71; 3.3	**1.93**	1.15; 3.25	**1.92**	1.11; 3.32
III: >120 mg/dl	**2.32**	1.4; 3.85	**2.29**	1.38; 3.8	**2.53**	1.46; 4.36
Waist circumference (cm)			1.012	0.995; 1.03	1.004	NS
C-reactive protein[b]					1.26	NS

Abbreviations: CI, confidence interval; DI, dyslipidemia; DM, diabetes mellitus; HT, hypertension; MS, metabolic syndrome; NS, nonsignificant; RR, relative risk. First number in parentheses denote number of subjects in model, second number the number of newly developed cardiometabolic disorder in the follow-up. Cardiometabolic disorders at baseline excluded. Bottom tertile of apo B (<95 mg/dl) served as reference (=RR 1.0) in each model. [a]Also adjusted for physical activity grade, family income category, and menopause, not significant for dependent variables, unless specifically indicated. [b]Log-transformed.

mediated largely by abdominal obesity in male subjects, in the female apo B modulated risk of hypertension independent of adiposity and low-grade inflammation. The development of diabetes among men reflected similar dynamics; the action of apo B was mediated fully by waist circumference, which seemed to incorporate the whole inflammatory component. In fact, CRP held in men a modest predictive ability independent of abdominal obesity only regarding dyslipidemia.

Based on the finding that apo B was the primary predictor of inflammatory markers in nondiabetic postmenopausal women among a variety of risk parameters including adiposity and IR,[6] the expressed suggestion that high apo B would be associated with elevated risk of developing CHD and diabetes, may be extended further to developing hypertension, dyslipidemia and MS and to men. In the current study, the predictive ability by apo B of 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 ~5–9% increment in RR) independent of waist circumference and apo B, whereas 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 MS and IR,[2] and small LDL particle number was best correlated with apo B (and triglycerides and HDL-cholesterol) in the Framingham Heart study.[22] Thus, presence of increased small, dense LDL particles may be related closely to the high predictive ability of cardiometabolic disorders by apo B in this population sample.

The present results are based on single measurements of studied variables at baseline, which overlook intraindividual variations. Yet, virtually all prospective studies use similar type of analyses, which would tend to underestimation of relative risks rather than to systematic bias. This analysis lacked testing apo B levels with another measure of inflammatory factor but CRP has been the most standardly used marker. Another limitation is the population sample in which MS is highly prevalent possibly precluding conclusions for other populations.

Conclusions

Over a nearly 6-year follow-up of a population sample, in which MS was highly prevalent, the development of high triglyceride-low HDL-cholesterol dyslipidemia and MS in both genders, as well as that of hypertension and diabetes in women, were each significantly predicted by age adjusted top tertile of apo B levels. Even the mid-tertile (95–120 mg/dl) exhibited significantly elevated cardiometabolic risk. This risk was independent of markers of abdominal obesity, subclinical inflammation and certain lifestyle variables. It is likely that the underlying increased small LDL particles and proinflammatory features account for the predictive ability by elevated apo B levels. To what extent these findings apply to populations with a lower prevalence of MS remains to be seen in future studies.

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References

1 Relimpio F, Losada F, Pumar A, Mangas MA, Morales F, Astorga R. Relationships of apolipoprotein B(100) with the metabolic syndrome in type 2 diabetes mellitus. *Diabet Res Clin Pract* 2002; **57**: 199–207.
2 Williams K, Sniderman AD, Sattar N, D'Agostino Jr R, Wagenknecht LE, Haffner SM. Comparisons of the associations of apolipoprotein B and low-density lipoprotein cholesterol with other cardiovascular risk factors in the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation* 2003; **108**: 2312–2316.
3 Muntner P, He J, Chen J, Fonseca V, Whelton PK. Prevalence of non-traditional disease risk factors among persons with impaired fasting glucose, impaired glucose tolerance, diabetes, and the metabolic syndrome: analysis of the Third National Health and Nutrition Examination Survey (NHANES III]. *Ann Epidemiol* 2004; **14**: 686–695.
4 Sniderman AD, St-Pierre AC, Cantin B, Dagenais GR, Despres JP, Lamarche B. Concordance/discordance between plasma apolipoprotein B levels and the cholesterol indexes of atherosclerotic risk. *Am J Cardiol* 2003; **91**: 1173–1177.
5 Sattar N, Williams K, Sniderman AD, D'Agostino Jr R, Haffner SM. Comparisons of the associations of apolipoprotein B and non-high-density lipoprotein cholesterol with other cardiovascular risk factors in the Insulin Resistance Atherosclerosis Study. *Circulation* 2004; **110**: 2687–2693.
6 Faraj M, Messier L, Bastard JP, Tardiff A, Godbout A, Prud'homme D *et al*. Apolipoprotein B: a predictor of inflammatory status in postmenopausal overweight and obese women. *Diabetologia* 2006; **49**: 1637–1646.
7 Dallongeville J, Cottel D, Arveiler D, Tauber JP, Bingham A, Wagner A *et al*. The association of metabolic disorders with the metabolic syndrome is different in men and women. *Ann Nutr Metab* 2004; **48**: 43–50.
8 Lind L, Vessby B, Sundstrom J. The apolipoprotein B/AI ratio and the metabolic syndrome independently predict risk for myocardial infarction in middle-aged men. *Arterioscler Thromb Vasc Biol* 2006; **26**: 406–410.
9 Wallenfeldt K, Bokemark L, Wikstrand J, Hulthe J, Fagerberg B. Apolipoprotein B/apolipoprotein A–I in relation to the metabolic syndrome and change in carotid artery intima-media thickness during 3 years in middle-aged men. *Stroke* 2004; **35**: 2248–2252.
10 Onat A, Ceyhan K, Başar Ö, Erer B, Toprak S, Sansoy V. Metabolic syndrome: major impact on coronary risk in a population with low cholesterol levels – a prospective and cross-sectional evaluation. *Atherosclerosis* 2002; **165**: 285–292.
11 Onat A, Avcı GŞ, Şenocak M, Örnek E, Gözükara Y. Plasma lipids and their interrelation in Turkish adults. *J Epidem Commun Health* 1992; **46**: 470–476.
12 Mather KJ, Hunt AE, Steinberg HO, Paradisi G, Hook G, Katz A *et al*. Repeatability characteristics of simple indices of insulin resistance: implications for research applications. *J Clin Endocrinol Metab* 2001; **86**: 5457–5464.
13 Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R *et al*. Expert committee on the diagnosis and classification of diabetes mellitus. Follow-up report on the diagnosis of diabetes mellitus. The expert committee on the diagnosis and classification of diabetes mellitus. *Diabet Care* 2003; **26**: 3160–3167.
14 Expert Panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Executive summary of the third report of the national cholesterol education program (NCEP). *JAMA* 2001; **285**: 2486–2497.
15 Grundy SM, Brewer HB, Cleeman JI, Smith SC, Lenfant C. Definition of metabolic syndrome: report of the national heart, lung, and blood institute/American heart association conference on scientific issues related to definition. *Circulation* 2004; **109**: 433–438.
16 Onat A, Hergenç G, Türkmen S, Yazıcı M, Sarı İ, Can G. Discordance between insulin resistance and metabolic syndrome: features and associated cardiovascular risk in adults with normal glucose regulation. *Metabolism* 2006; **55**: 445–452.
17 Onat A, Uyarel H, Hergenç G, Karabulut A, Albayrak S, Can G. Determinants and definition of abdominal obesity as related to risk of diabetes, metabolic syndrome and coronary disease in Turkish men: a prospective cohort study. *Atherosclerosis* 2006; May 5, E-pub).
18 Sniderman A, Scantlebury T, Cianflone K. Hypertriglyceridemic hyperapoB: the unappreciated atherogenic dyslipoproteinemia in type 2 diabetes mellitus. *Ann Intern Med* 2001; **135**: 447–459.
19 Leino A, Impivaara O, Kaitsaari M, Jarvisalo J. Serum concentrations of apolipoprotein A–I, apolipoprotein B, and lipoprotein(a) in a population sample. *Clin Chem* 1995; **41**: 1633–1636.
20 Sung KC, Hwang ST. Association between insulin resistance and apolipoprotein B in normoglycemic Koreans. *Atherosclerosis* 2005; **180**: 161–169.
21 Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A–I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet* 2001; **358**: 2026–2033.
22 Kathiresan S, Otvos JD, Sullivan LM, Keyes MJ, Schaefer EJ, Wilson PWF *et al*. Increased small low-density lipoprotein particle number: a prominent feature of the metabolic syndrome in the Framingham Heart Study. *Circulation* 2006; **113**: 20–29.