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Serum C-reactive protein is an independent risk factor predicting cardiometabolic risk

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Abstract

The aim of the study was to investigate the role of serum C-reactive protein (CRP) level as a risk factor in predicting metabolic syndrome (MS), hypertension, atherogenic dyslipidemia, type 2 diabetes mellitus, and coronary heart disease. We prospectively evaluated 1270 men and 1320 women, aged 30 to 89 years, who had serum CRP determinations and a mean 4.3 years' follow-up. The CRP values were log-transformed for calculations. Metabolic syndrome was defined by the Adult Treatment Panel III criteria modified for male abdominal obesity. Prediction of outcome was performed by excluding from analysis the particular outcome variable existing at baseline examination. Smoking men had higher age-adjusted estimated CRP concentrations ($P < .001$), whereas smoking women had lower CRP ($P = .027$) than never smokers. Risk of developing an elevated (≥2 mg/L) CRP was predicted significantly by baseline CRP in both sexes and by apolipoprotein (apo B), current smoking, and family income in men, when adjusted for 5 further variables. Baseline CRP levels predicted atherogenic dyslipidemia when adjusted for age, baseline dyslipidemia values, and apo B tertiles and predicted incident hypertension independent of age, waist circumference, and smoking status. After adjustment for sex, age, and the 5 MS components, CRP predicted newly developing MS, with a hazard ratio (HR) of 1.16 (95% confidence interval, 1.02-1.32). When adjusted for sex, age, baseline glucose, waist circumference, and apo B tertiles, diabetes was significantly predicted by CRP in women (HR, 1.31) alone. Sex- and age-adjusted CRP level identified also those that progressed to diabetes independent of a fasting glucose >100 mg/dL (HR, 1.39; 95% confidence interval, 1.21-1.59), although not in men. In the prediction of incident coronary heart disease, CRP contributed to 7 established risk factors including waist circumference with a significant 1.18-fold HR. C-reactive protein is both an independent significant predictor and a risk factor of cardiometabolic risk among Turkish adults, additive to MS components, whereby risk is modulated by sex, smoking habit, and apo B.

1. Introduction

Serum concentrations of the acute phase reactant C-reactive protein (CRP) have been recognized in the past decade as a consistent marker of developing coronary heart disease (CHD), thus linking low-grade systemic inflammation with atherosclerosis. Prospective data from epidemiologic studies disclosed a significant relationship between CRP and future CHD risk in apparently healthy men [1-3] and women [4,5]. Elevated levels of CRP offer predictive value exceeding that of low-density lipoprotein (LDL) cholesterol [6]. Nonetheless, absence of a relationship of CRP with risk of myocardial infarction has also been reported in men when comprehensive adjustment was made for established risk factors [7].

Low-grade inflammation has been postulated to be linked also to the development of metabolic disorders; and some prospective epidemiologic evidence has been accumulated regarding diabetes [8,9], hypertension [10-12], and MS [8,9]. However, this may still be considered as scarce. Positive relationships between the risk of developing hypertension and elevated CRP levels were reported recently in men [11] and women [12]. Prospective studies linking inflammation with MS have also been few [8,9,13], especially among women; and a recent study using a mendelian randomization approach suggested that CRP is causally not related to MS in British women [14].

When the predictors of inflammatory markers (interleukin 6, CRP, tumor necrosis factor-α, and others) in 77

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nondiabetic postmenopausal overweight and obese women were investigated, apolipoprotein (apo) B was found to be the primary predictor among a variety of risk parameters (adiposity, blood pressure [BP], insulin resistance, triglycerides, apo B/apo A-I ratio, Framingham risk points, etc) [15]. Among Turkish adults who have a high prevalence of metabolic syndrome (MS) [16], apo B appears to be independently related not only to incident CHD but also to hypertension, MS, and diabetes [17]. Moreover, a diverging effect of current smoking among female and male Turks emerges on certain major metabolic disorders [18], which necessitates the examination of its role in the development of raised CRP and its modifying influence on the CRP-related cardiometabolic risk.

Underscoring the inability to separate hypertension from the injurious agents that initiate arterial inflammation, such as cigarette smoking and agents of metabolic origin, it was pointed out in a recent editorial that research is moving toward the interface between inflammation and metabolic disturbances, which is where arterial disease occurs [19]. It is therefore worth addressing the pathways from low-grade inflammation to metabolic disorders such as atherogenic dyslipidemia, hypertension, MS, and diabetes and to CHD prospectively in a suitable cohort. The present article investigates longitudinally the following issues in a cohort representative of Turkish adults [20]: (*a*) Which risk parameters determine risk for developing an elevated CRP? (*b*) To what extent are CRP levels associated with the development of the stated cardiometabolic risks? (*c*) Finally, do sex, smoking habit, and apo B, another agent with prominent proinflammatory properties, modulate the stated risks? This article discloses novel findings related to the prediction by CRP of atherogenic dyslipidemia, hypertension, and MS and to the modulation of CRP-related risk by sex, female-specific smoking, and apo B.

2. Methods

2.1. Population sample

The Turkish Adult Risk Factor Study is a prospective cohort study 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 [20]. It involves a random sample of the Turkish adult population representatively stratified for sex, age, geographical regions, and rural-urban distribution [20]. Measurements of CRP were first performed at the survey of 2000, which formed the baseline. Participants were 30 years of age or older. Of the survivors, 7% were examined up to the survey of 2001-2002 and 12% up to 2003-2004, the remainder having been examined lastly in the survey of 2005-2006. Serum CRP was measured in 2709 men and women at baseline. Exclusion of 5 individuals having age >89 years and 114 persons with CRP values >15 mg/L (given that extreme CRP values are usually not associated with cardiometabolic disorders) limited the study sample to 2590 adults (1270 men and 1320 women). Nearly 90% of baseline participants of the present and the previously reported prospective study [17] 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 was 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 12-lead electrocardiogram (ECG).

2.2. Measurements of risk variables

A history of infection in the month preceding the survey or of systemic inflammation was not elicited. Blood pressure was measured in the sitting position on the right arm, and the mean of 2 recordings at least 3 minutes 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; Roche Diagnostics, Mannheim, Germany), with the subject standing and wearing only underwear, at the level midway between the lower rib margin and the iliac crest. Body mass index was calculated as weight divided by height squared (in kilograms per square meter). Self-reported cigarette smoking status was categorized into nonsmokers, former smokers, and current smokers.

Plasma concentrations of cholesterol, fasting triglycerides, high-density lipoprotein (HDL) cholesterol, and glucose were determined at baseline examination by the enzymatic dry chemistry method using a Reflotron apparatus (Roche Diagnostics). The LDL cholesterol values were computed according to the Friedewald formula. In the final 3 surveys, the stated parameters as well as apo B, insulin, and CRP values were assayed in a single central laboratory. Blood samples were spun at 1000*g* for 10 minutes and shipped within a few hours on cooled gel packs at 2°C to 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). Concentrations of serum CRP and apo B were measured by the Behring nephelometry, CRP using an N high-sensitivity CRP kit (Behring Diagnostics, Marburg, Germany) the lower detection limit of which was 0.175 mg/L. Within-run and day-to-day coefficients of variation for CRP were 1.3% and 2.9%, respectively. External quality control was performed with a reference laboratory in a random selection of 5% to 6% of participants. Data on insulin and apo B

were available in two thirds of the participants, and measurements of the studied parameters were available again in their final examination.

2.3. Definitions and outcomes

Individuals with *diabetes* were diagnosed with the criteria of the American Diabetes Association [21], namely, plasma fasting glucose ≥126 mg/dL (or 2-hour postprandial glucose >200 mg/dL) and/or current use of diabetes medication. Individuals with *metabolic syndrome* were identified when 3 out of the 5 criteria of the National Cholesterol Education Program (Adult Treatment Panel III) [22] were met, modified for prediabetes (fasting glucose 100-125 mg/dL) [23] and further for abdominal obesity using as cutpoint ≥95 cm in men, as recently assessed in the Turkish Adult Risk Factor study [24,25]. *Atherogenic dyslipidemia* (or simply *dyslipidemia*) referred to the combined presence of high triglyceride (≥150 mg/dL) and low HDL cholesterol (<40/<50 mg/dL) values as defined by the Adult Treatment Panel 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 3 criteria was required, and the MS and/or dyslipidemia status of the subsequent survey was adopted in few individuals presenting 2 positive criteria. Apolipoprotein B cutoff by 120 and 95 mg/dL yielded 519, 381, and 405 (of 1305) men and women in the top, middle, and bottom brackets (40%, 29%, and 31%). Homeostatic model assessment (HOMA) was calculated with the following formula [26]: insulin (in milli–international units per liter)* glucose (in millimoles per liter)/22.5.

Diagnosis of nonfatal CHD was based on the presence of angina pectoris, a history of myocardial infarction with or without accompanying Minnesota codes of the ECG [27], or a history of myocardial revascularization. Typical angina and, in women, age >45 years were prerequisite for a diagnosis when angina was isolated. The ECG changes of "ischemic type" of greater than minor degree (codes 1.1-2, 4.1-2, 5.1-2, 7.1) were considered as myocardial infarct sequelae or myocardial ischemia, respectively. Cause of death was assigned based on information elicited from first-degree relatives and local health center staff, taking into account preexisting clinical and laboratory findings obtained during the biennial follow-ups. Fatal CHD comprised death from heart failure and fatal coronary event.

2.4. Data analysis

Because of the skewed distribution of concentrations of insulin and CRP, these were log-transformed for calculations. Descriptive parameters were shown as mean ± SD or as age-adjusted estimated mean ± SE and in percentages. Two-sided t tests and Pearson χ^2 tests were used to analyze the differences between means and proportions of other groups; univariate analyses followed by pairwise comparisons were made to detect significance between estimated marginal means in smoking groups. Multiple linear regression analyses were performed with continuous parameters. In the prediction of a dependent variable, the cohort in whom that particular variable existed at baseline examination was excluded from the multivariate analysis. Estimates (and 95% confidence intervals [CIs]) for relative risk (RR) of a dependent variable were obtained by use of logistic regression analysis in models that controlled for potential confounders. Hazard ratios (HRs) were calculated using the given RRs for 1 SD (SD = 2.85-fold concentration of CRP). A value of $P < .05$ on the 2-tailed test was considered statistically significant. Statistical analyses were performed using SPSS 10 for Windows (SPSS, Chicago, IL, no. 9026510).

3. Results

At baseline examination, mean age of 2590 participants was 49.8 ± 12 years; and mean follow-up constituted 4.3 years (total 11 100 person-years). Excluded from prospective analysis of outcomes were cases of prevalent CHD or each metabolic disorder, respectively.

3.1. Stratification of CRP values by sex and smoking status

Table 1 summarizes the baseline risk characteristics of the study sample in men and women, which indicate the presence of wide waist girth, comparatively low total and HDL cholesterol levels, and high levels of apo B relative to LDL cholesterol. Age-adjusted estimated marginal means

Table 1
Risk characteristics at baseline, by sex

	Men (n = 1270)			Women (n = 1320)		
	n	Mean	SD	Mean	SD	P
Age (y)		50.0	12.2	49.6	12	NS
Waist circumference (cm)		94.1	10.9	90.5	12.5	*
Systolic BP (mm Hg)		126.9	21.9	131.6	25.4	*
Diastolic BP (mm Hg)		80.9	13.0	82.4	13.9	**
Total cholesterol (mg/dL)		181	37.2	187.6	40.8	*
HDL cholesterol (mg/dL)		37.2	11.7	44.7	12.7	*
LDL cholesterol (mg/dL)	2285	113.8	31.8	119.4	34.9	*
Fasting triglycerides (mg/dL)	2216	155.3	99.3	132.6	85.1	*
Fasting glucose (mg/dL)	2198	99.0	29.3	100.4	28.0	NS
Apo B (mg/dL)	1768	115.0	36.4	112.8	36.2	NS
Fasting insulin[a] (mIU/L)	1674	7.7	2.1	7.8	2.0	NS
CRP[a] (mg/L)		1.77	2.7	2.03	2.9	*
Current/former smoking (%)		52.7/20.5		18.0/3.6		*

Unspecified n equals to 2590. P values > .2 denoted by NS. NS indicates not significant.

[a] Geometric mean values.

* $P < .001$.

** $P < .005$.

Table 2
Age-adjusted serum CRP estimated marginal mean values (in milligrams per liter) at baseline, by smoking status

	Men			Women		
		Geometric mean	SE		Geometric mean	SE
	1270	1.77		1320	2.04	
Never smokers	340	1.52	1.05	1035	2.08	1.03
Former smokers	260	1.67	1.06	48	2.70**	1.16
Current smokers	670	1.96*	1.04	237	1.75*	1.07

* Different ($P < .03$) from never smokers.
** $P = .085$ from never smokers.

(±SE) among male and female subjects by smoking status are shown in Table 2. Smoking men had higher CRP concentrations ($P < .001$), whereas smoking women had lower CRP ($P = .027$) than never smokers.

3.2. Determinants at baseline of subsequent elevated CRP

Paired values of CRP at baseline and final surveys were available in 1487 participants (57.4%). When 47.7% of individuals who had serum CRP values ≥2.0 mg/L at baseline examination were excluded from analysis, determinants at baseline were sought for the prediction of CRP values ≥2.0 mg/L developing among 777 adults in the follow-up. Fasting insulin and apo B levels were available in just over half the sample. Logistic regression analysis was carried out in a model that comprised age, waist circumference, smoking status, family income, systolic BP, apo B, HDL cholesterol, fasting insulin, and baseline CRP concentrations in 412 subjects (Table 3). Baseline CRP was the significant predictor of subsequently elevated CRP in each sex, whereas current smoking, apo B, and family income were so additionally in men. Current smoking was not a determinant of elevated CRP levels in women. Measure of agreement of self-reported categories of smoking was tested separately in men and women between the baseline and subsequent surveys and between the final and the preceding surveys: κ values regarding female smoking status averaged 0.80 ($P < .001$), compared with 0.76 ($P < .001$) in men.

3.3. Prediction of atherogenic dyslipidemia and hypertension

Of those having serum triglyceride determinations at baseline, 27% who met the criteria of atherogenic dyslipidemia were excluded from analysis. Log CRP adjusted for sex, age, and baseline concentrations of HDL cholesterol and triglycerides was associated with future dyslipidemia developing in 178 subjects of 988 men and women (RR, 2.00; 95% CI, 1.33-3.03) (Table 4). Significance persisted in separate sexes (in 409 men: RR, 2.13; 95% CI, 1.10-4.12; in 579 women: RR, 1.78; 95% CI 1.03-3.06). After additional adjustment for apo B tertiles, CRP retained significance (RR, 1.76; 95% CI, 1.05-2.94) but not in separate sexes.

Out of 2125 nonhypertensive persons at baseline, 786 subjects (37%) developed hypertension in the follow-up. Sex- and age-adjusted RR of CRP for new hypertension was 1.62 (95% CI, 1.31-2.01), which proved similarly significant ($P < .007$) in both sexes: 1.54 in men and 1.70 in women. When waist circumference was included in the regression analysis, RR attenuated to 1.29 but remained significant (95% CI, 1.03-1.62) in combined sexes. Introduction of smoking status marginally increased RR to 1.32 (95% CI, 1.05-1.65) and also RR in men to a significant 1.41 (95% CI, 1.02-1.95).

3.4. Prediction of MS and diabetes by CRP

Among 1090 persons free of MS at baseline, 284 subjects (26%) developed MS in the follow-up. After adjustment for sex, age, and baseline values of all 5 MS components (waist circumference, HDL cholesterol, triglycerides, systolic BP, and glucose) as continuous variables, MS was predicted with an RR of 1.53 (95% CI, 1.06-2.19) by CRP (Table 4). All standard components predicted MS significantly (data not shown). With the addition of apo B tertiles (determined in part of the sample) to the previous regression model, the odds of the association of CRP were unchanged (1.53); but the CI widened (95% CI, 0.98-2.42). It became stronger in men and attenuated in women.

Log CRP, adjusted for sex, age, baseline waist circumference, and fasting glucose, in 2089 nondiabetic individuals was a significant predictor of diabetes developing in 174 subjects (RR, 2.10; 95% CI, 1.38-3.20). Significant prediction was observed not in men (RR, 1.50; $P = .17$) but only in women (RR, 3.05; 95% CI, 1.64-5.70) (Table 4). When apo B tertiles were added to the model, RR in sexes combined attenuated to only 1.70 (95% CI, 1.04-2.78) and persisted to be significant in women (RR, 2.15; 95% CI, 1.05-4.39). Sex- and age-adjusted CRP level also identified progression to diabetes in participants with a fasting glucose level >100 mg/

Table 3
Prediction of CRP value ≥2 mg/L by determinants in subjects free of elevated CRP at baseline

	Men (n = 212)		Women (n = 200)	
	RR	*P*	RR	*P*
Age (y)	1.007	NS	0.991	NS
Baseline CRP[a]	**10.0**	.005	**23.9**	.0005
Waist circumference (cm)	1.027	.114	0.986	NS
Current smokers	**2.25**	.045	1.006	NS
Former smokers	1.41	NS	3.11	NS
Apo B (mg/dL)	**1.010**	.027	0.994	NS
HDL cholesterol (mg/dL)	1.000	NS	0.984	NS
Systolic BP (mm Hg)	0.995	NS	1.009	NS
Family income (I-IV)	**0.74**	.047	0.936	NS
Fasting insulin[a]	0.81	NS	2.23	.18

Sixty-seven men and women each developed CRP ≥2 mg/L in follow-up. Model comprised 90 male and 30 female current smokers. Significant relative risks are highlighted in bold.
[a] Log-transformed values.

Table 4
Adjusted RRs in the prediction of various metabolic disorders by baseline serum CRP values[a]

	Model	n	Total		Men		Women	
			RR	95% CI	RR	95% CI	RR	95% CI
Atherogenic dyslipidemia	1a	988	**2.00**	1.33-3.03	**2.13**	1.10-4.12	**1.78**	1.03-3.06
	2	652	**1.76**	1.05-2.94	2.25	0.98-5.18	1.46	0.76-2.86
Hypertension	1b	2125	**1.29**	1.03-1.62	1.32	0.96-1.82	1.30	0.94-1.80
	2	2125	**1.32**	1.05-1.65	**1.41**	1.02-1.95	1.30	0.94-1.80
Type 2 diabetes mellitus	1c	2089	**2.10**	1.38-3.20	1.50	0.84-2.68	**3.05**	1.64-5.70
	2	1425	**1.70**	1.04-2.78	1.32	0.66-2.61	**2.15**	1.05-4.39
	3	2089	**2.53**	1.72-3.73	1.53	0.89-2.61	**4.30**	2.40-7.69
	4	661	**2.44**	1.19-5.02	1.92	0.61-6.08	**2.85**	1.10-7.37
MS	1d	1090	**1.53**	1.06-2.19	1.56	0.92-2.67	**1.69**	1.01-2.82
	2	725	1.53	0.98-2.42	1.94	0.97-3.86	1.58	0.84-2.99

Developing incident disorders in model 1: dyslipidemia, 73 men and 105 women; hypertension, 391 men and 395 women; diabetes, 90 men and 84 women; MS, 141 men and 143 women. Adjustments in model 1: sex, age; a: triglycerides, HDL cholesterol; b: waist circumference; c: waist circumference, fasting glucose; d: all 5 MS components. Model 2: apo B tertiles, additional to model 1a, c, and d. Smoking status in hypertension (1b). Model 3: sex, age, fasting glucose >100 mg/dL. Model 4: sex, age, log HOMA. Significant relative risks are highlighted in bold.

[a] Log-transformed values.

dL (RR, 2.53; 95% CI, 1.72-3.73; corresponding HR, 1.39; 95% CI, 1.21-1.59), although it was significant only in women (Table 4). In a subset of the cohort in whom HOMA index was available at baseline, CRP similarly predicted the development of diabetes in the whole sample and in women. Finally, among 999 subjects with known adiponectin concentrations at the final survey, baseline CRP predicted diabetes (RR, 3.30; 95% CI, 1.5-5.57) independent of the reciprocal association (P = .038) of adiponectin. Overall, 1.3% of subjects converted to diabetes per year; and Kaplan-Meier estimates in an up to 6-year follow-up showed that participants with CRP values ≥2.0 mg/L had significantly lower probability of remaining free of diabetes (89.6%) than those with <2.0 mg/L (95.0%, log rank P < .0001) (Fig. 1).

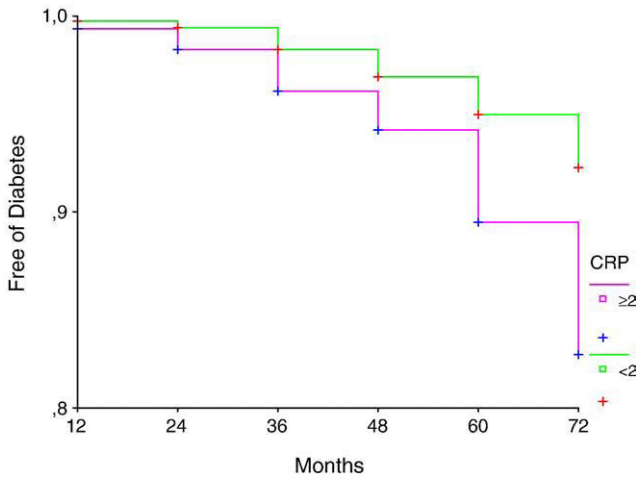

Fig. 1. Kaplan-Meier estimates of development of type 2 diabetes mellitus over 6-year follow-up, stratified by 1189 participants with normal (<2.0 mg/L) and 1109 with elevated (≥2.0 mg/L) CRP. A total of 60 and 116 subjects, respectively, were identified as having converted to diabetes.

3.5. Prediction of CHD

In a model comprising sex, age, waist girth, systolic BP, smoking status, fasting glucose, and HDL cholesterol in 2128 participants, log CRP predicted incident CHD independently in both sexes combined (RR, 1.61; 95% CI, 1.13-2.29; corresponding to an HR of 1.18; 95% CI, 1.04-1.34). Similar magnitude of associations in separate sexes remained at borderline significance (Table 5).

4. Discussion

In this prospective cohort study representative of Turkish adults, we found that smoking status, apo B levels, and low family income were major determinants of subsequently elevated CRP levels, albeit only in men. Increasing CRP levels significantly predicted in both sexes combined atherogenic dyslipidemia independently, subsequent hypertension irrespective of waist circumference, and subsequent

Table 5
Prediction of CHD by baseline serum CRP and certain traditional risk factors

	Total (n = 2128)		Men (n = 1017)		Women (n = 1111)	
	RR	P	RR	P	RR	P
Sex (female)	1.08	NS				
Age (y)	**1.06**	.0005	**1.055**	.0005	**1.063**	.0005
Waist circumference (cm)	1.012	.072	1.016	.13	1.011	.25
Systolic BP (mm Hg)	**1.015**	.0005	**1.016**	.002	**1.014**	.001
Fasting glucose (mg/dL)	**1.005**	.012	1.006	.052	1.005	.11
CRP[a]	**1.65**	.008	1.61	.069	1.57	.07
HDL cholesterol (mg/dL)	0.992	.21	1.000	NS	0.987	.12
Former smokers	1.40	.15	**1.86**	.028	0.73	NS
Current smokers	1.08	NS	1.46	.17	0.78	NS

One hundred nineteen men and 131 women developed incident CHD in follow-up. Significant relative risks are highlighted in bold.

[a] Log-transformed values.

MS, after adjustment for all 5 components. The CRP levels were a predictor of future diabetes in women regardless of baseline fasting glucose, waist circumference, and apo B, and of incident CHD in both sexes combined, independent of sex, age, and other relevant confounders. Thus, CRP levels were independently predictive of cardiometabolic risk, whereas sex, smoking habit, and apo B levels appeared to modulate the CRP-related risk.

To estimate the magnitude of the contribution of the risk involved with raised CRP levels, it should be kept in mind that the difference in median values between the top and the bottom quintiles, that is, between the 90th and the 10th percentiles, spanned a 15-fold gradient (7.5 vs 0.5 mg/L) in this population sample, like other populations. An RR of 1.7 across a gradient of 1 log CRP corresponds to an HR of 1.21, and an RR of 1.3 to an HR of 1.09 to 1.10 related to the outcome of individual cardiometabolic disorders. The contributed risk by the inflammatory component was modest when compared with HRs of waist circumference (2.02) or fasting triglyceride (1.88) derived from the identical multivariate model, but the risk was additive to that of the components or other risk factors and was of substantial magnitude particularly with respect to CHD.

This is the first documented study in which CRP predicted future MS, independent of age and the 5 components. Of the previous 3 prospective studies that did not fully adjust for the MS components, in the one on a Mexican population sample, with MS being defined in the absence of abdominal obesity, CRP was found to be a predictor in women but not in men [8]; and the reverse, namely, prediction of MS by rising CRP tertiles, was detected in men but not in women [13]. The risk of MS was several-fold higher with elevated CRP concentrations in the Finnish study that was confined to men [9].

4.1. Sex and smoking modify level and effect of CRP

Sex interacted in the predictors of elevated CRP levels and in the association of serum CRP with future diabetes risk after adjustment for age and relevant confounders. Current smoking, apo B levels, and family income were determinants of the inflammatory marker in men alone. Relationships of CRP levels with waist circumference, BP, and serum apo B, stronger in women than in men in univariate correlations (data not shown), were modified on multivariate analysis by smoking. Our findings in men are in line with the fact that cigarette smoking predicts inflammation [11,28]; associations with various markers of inflammation were generally lacking in women in the large cross-sectional multinational MONItoring of trends and determinants in CArdiovascular disease (MONICA) Augsburg study [28]. Whereas elevated CRP levels were significantly predicted by current smoking in men, a neutral effect was apparent in women, among whom age-adjusted current smokers exhibited even significantly lower CRP concentrations than never smokers. Lack of an induced inflammatory effect was remarkably independent not only of a marker of central obesity and fasting insulin, but also of family income, a surrogate of socioeconomic level.

We recently reported evidence that smoking protects Turks from obesity [25] and women from MS and diabetes [18], an effect which was independent of central obesity and hyperinsulinemia—and partly of serum CRP either. C-reactive protein is recognized to exert anti-inflammatory mechanisms, inasmuch as the direct interaction between CRP and complement can both activate and inhibit inflammation in atherosclerotic lesions [29]. The full reasons for this “protective” effect of smoking in Turkish women, an indication of which had previously been noted [30], remain unclear; but it seemingly results from a combination of reducing effects of smoking on abdominal obesity and on serum asymmetric dimethylarginine levels, lack of an inflammatory effect, and enhancement of serum preheparin lipoprotein mass (unpublished observations).

4.2. CRP, a risk factor for metabolic disorders, modified by apo B levels

Although prospective population-based data on the prediction of atherogenic dyslipidemia by CRP are lacking, 2 studies addressed the development of hypertension. In agreement with the positive relationships between baseline CRP and subsequent development of hypertension in women [12] and in men [11], CRP emerged as an independent predictor of hypertension in the present study. In the prediction of hypertension; high-triglyceride, low-HDL dyslipidemia; and MS, CRP, and apo B levels appeared to affect risk independently in men, whereas apo B and aging (menopause) were factors in women that mediated inflammation in the development of dyslipidemia. Independent of plasma glucose, CRP contributed significantly to the development of diabetes in women, additive to waist circumference and to apo B, whereas the potential influence of inflammation seemed minor in men. C-reactive protein contributed to new diabetes in women also regardless of a measure of insulin resistance or adiponectin; thus, it should not be considered merely a marker of fatness.

4.3. Independent predictive value of CRP for CHD risk

In predicting future CHD, the top CRP tertile (>3 mg/L) is expected to yield a mean multiple-adjusted RR of 2.0 according to a consensus Centers for Disease Control and Prevention/American Heart Association statement [31] or 1.45 in an updated meta-analysis [4]. Our estimated RR of 1.65 of log CRP is in close agreement with the cited meta-analysis because a CRP gradient across tertiles of the general population usually spans some 8-fold values.

Cardiometabolic risk is driven by adiposity (waist girth as marker), systemic inflammation (CRP), and small dense LDL (apo B), which are undoubtedly interrelated and related to insulin resistance. Based on this study and on separate analyses on apo B, waist girth appears to be dominant in regard to dyslipidemia, hypertension, and diabetes, with apo B or CRP, respectively, modulating the risk [17].

Development of CHD is driven by apo B, with CRP independently contributing in the risk. All 3 components are involved in the risk of MS independently. Smoking is likely an element in further modulating this risk on a sex-specific basis. Implications of this knowledge include the potential targeting of the treatment in various cardiometabolic disturbances in the future.

Like most similar prospective studies, single CRP measurements at baseline were used herein; but the weight of this potential limitation is relatively small in view of the recognized stability of this protein over a long follow-up [31]. The substitution of data of the subsequent survey for missing fasting measurement of serum triglycerides in a small proportion is not expected to substantially influence the results. Good agreement of and similarity between sexes in self-reported categories of smoking status render a potential substantial bias in female reporting highly unlikely. Unmeasurable confounding cannot be ruled out but is very unlikely in view of appropriate multiple adjustments performed. The strengths of the study include its being based on a representative sample of a general population, incorporation of women, prospective design and appropriate follow-up period, and measurement of studied parameters such as BP and plasma glucose.

We conclude that cigarette smoking, apo B levels, and family income are important determinants of serum CRP increments in the long term in Turkish men, independent of waist girth. Elevated CRP levels predict significantly future cardiometabolic risk pertaining to atherogenic dyslipidemia, hypertension, MS, diabetes, and incident CHD, independent of age, apo B, and other relevant confounders. These observations further support the concept of low-grade inflammation being critical in the development of the metabolic disturbances as well as of CHD. Sex and/or smoking habit is an important modifier of CRP concentrations; and serum apo B levels, by partly mediating CRP, modulate the cardiometabolic risk.

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References

[1] Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973-9 [Erratum, N Engl J Med 1997;337:356].

[2] Koenig W, Sund M, Fröhlich M, et al. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA Augsburg cohort study, 1984 to 1992. Circulation 1999;99:237-42.

[3] Pirro M, Bergeron J, Dagenais GR, et al. Age and duration of follow-up as modulators of the risk for ischemic heart disease associated with high plasma C-reactive protein levels in men. Arch Intern Med 2001;161:2474-80.

[4] Danesh J, Wheeler JG, Hirschfield GM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease: prospective study and updated meta-analysis. N Engl J Med 2004;350:1387-97.

[5] Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836-43.

[6] Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347:1557-65.

[7] Doggen CJ, Berckmans RJ, Sturk A, Manger Cats V, Rosendaal FR. C-reactive protein, cardiovascular risk factors and the association with myocardial infarction in men. J Intern Med 2000;248:406-14.

[8] Than TS, Sattar N, Williams K, Gonzales-Villapando C, Lean MEJ, Haffner SM. Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City Diabetes Study. Diabetes Care 2002;25:2016-21.

[9] Laaksonen DE, Niskanen L, Nyyssonen K, et al. C-reactive protein and the development of metabolic syndrome and diabetes in middle-aged men. Diabetologia 2004;47:1403-10.

[10] Engström G, Janzon L, Berglund G, et al. Blood pressure increase and incidence of hypertension in relation to inflammation-sensitive plasma proteins. Arterioscler Thromb Vasc Biol 2002;22:2054-8.

[11] Niskanen L, Laaksonen DE, Nyyssonen K, et al. Inflammation, abdominal obesity, and smoking as predictors of hypertension. Hypertension 2004;44:859-65.

[12] Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. JAMA 2003;290:2948-51.

[13] Cifkova R, Frohlich J, Skodova Z, et al. C-reactive protein and the risk of developing the metabolic syndrome. A population study. Eur Heart J Suppl 2005;26:445.

[14] Timpson NJ, Lawler DA, Harbord RM, et al. C-reactive protein and its role in metabolic syndrome: mendelian randomisation study. Lancet 2005;366:1954-9.

[15] Faraj M, Messier L, Bastard JP, et al. Apolipoprotein B: a predictor of inflammatory status in postmenopausal overweight and obese women. Diabetologia 2006;49:1637-46.

[16] 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;165:285-92.

[17] Onat A, Can G, Hergenç G, Yazıcı M, Karabulut A, Albayrak S. Serum apolipoprotein B predicts dyslipidemia, metabolic syndrome and, in women, hypertension, diabetes, independent of markers of central obesity and inflammation. Int J Obes 2007;31:1119-25.

[18] Onat A, Özhan H, Esen AM, et al. Prospective epidemiologic evidence of a “protective” effect of smoking on metabolic syndrome and diabetes among Turkish women—without associated overall health benefit. Atherosclerosis 2007;193:380-9.

[19] Grundy SM. Inflammation, hypertension, and the metabolic syndrome. JAMA 2003;290:3000-2.

[20] Onat A. Risk factors and cardiovascular disease in Turkey. Atherosclerosis 2001;156:1-10.

[21] Genuth S, Alberti KG, Bennett P, et al. Follow-up report on the diagnosis of diabetes mellitus. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2003; 26:3160-7.

[22] 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;285:2486-97.

[23] 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;109:433-8.

[24] 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;55:445-52.

[25] 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 2007;191:182-90.

[26] Mather KJ, Hunt AE, Steinberg HO, et al. Repeatability characteristics of simple indices of insulin resistance: implications for research applications. J Clin Endocrinol Metab 2001;86:5457-64.

[27] Rose G, Blackburn H, Gillum RF, Prineas RJ. Cardiovascular survey methods. 2nd ed. Geneva: WHO; 1982. p. 124-7.

[28] Fröhlich M, Sund M, Löwel H, Imhof A, Hoffmeister A, Koenig W. Independent association of various smoking characteristics with markers of systemic inflammation in men: results from a representative sample of the general population (MONICA Augsburg Survey 1994/1995). Eur Heart J 2003;24:1365-72.

[29] Paffen E, deMaat MPM. C-reactive protein in atherosclerosis: a causal factor? Cardiovasc Res 2006;71:30-9.

[30] Onat A, Sansoy V, Yıldırım B, Keleş İ, Uysal Ö, Hergenç G. C-reactive protein and coronary heart disease in western Turkey. Am J Cardiol 2001;88:600-7.

[31] Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease. Application to clinical and public health practice. A statement for health care professionals. From the Centers of Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499-511.