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Serum complement C3: a determinant of cardiometabolic risk, additive to the metabolic syndrome, in middle-aged population

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Abstract

We studied whether serum complement C3 (C3) is an independent determinant of incident cardiometabolic risk (coronary heart disease [CHD], metabolic syndrome [MetS], and type 2 diabetes mellitus). A cohort of 1220 adults of a general population (age, 53 ± 10.5 years) was evaluated prospectively at 3.3 years follow-up using Cox proportional hazard regressions. Cardiometabolic risk factors were measured. Metabolic syndrome was identified by Adult Treatment Panel III criteria modified for male abdominal obesity. The C3 levels were associated significantly and linearly with serum triglycerides, waist circumference, and C-reactive protein (CRP), and inversely with current smoking but not with the marker of insulin resistance. In regression models for incident MetS, increasing C3 quartiles strongly predicted MetS in women and in both sexes combined after adjusting for all 5 MetS components and other confounders. Circulating C3 significantly predicted in each sex incident CHD independent of age, smoking status, and presence of MetS. Even after entering CRP, C3 predicted CHD with a relative risk of 1.35 (95% confidence interval, 1.09-1.67) for 1-SD increment of C3 in the total sample. Complement C3 tended to contribute, additively to MetS, to the association with diabetes with a relative risk of 1.36 in women alone, not in men. In conclusion, elevated serum complement C3 is part of the MetS cluster and confers CHD risk, additively to MetS components and CRP, in a population in which MetS prevails. Levels contribute, additively to MetS, to the diabetes risk in women alone.

1. Introduction

Complement C3 (C3) is an acute-phase reactant produced by the liver, a cytokine secreted by activated macrophages at inflammation sites and by adipocytes [1], and has a central role in the immune system [2]. Complement C3 has been associated with atherosclerosis and cardiovascular risk factors [3,4]. It is not established whether acute-phase proteins including C3 are merely practical markers of vascular disease or whether, induced by cytokines, they may play some active role in atherothrombosis [5,6]. Prospective studies on the associations of C3 with coronary heart disease (CHD) are few [7-9]. Complement C3 has been recently identified as predicting coronary or cardiovascular events but not independently of the established risk factors [8]. Conversely, in a brief follow-up of 148 patients with acute coronary syndrome, the complement C3/C4 ratio emerged as a risk factor for recurrent cardiovascular events with an odds ratio (OR) of 1.33 (1.08-1.63) after adjustment for traditional risk factors [9]. In patients with coronary artery disease, complement protein has been observed to be deposited and activated in the vessel wall [10].

The complement system is activated in postprandial lipemia, and chylomicrons stimulate adipocyte C3 production via activation of the alternative complement cascade. Yet, the pathophysiologic role of C3 in metabolic syndrome (MetS) and diabetes remains unclear. It has been stated that C3 concentrations may play an important role in the expression of MetS, and future population-based studies are needed to clarify whether C3 can help identify subjects at risk of developing MetS [11]. Moreover, a lipogenic role of

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C3 in fatty acid metabolism was reported [1]. Inflammatory markers have been found to cluster with established components of MetS [12], and the proinflammatory state is recognized to be linked to MetS [13]. Moreover, C3 was found to be a stronger inflammatory marker of insulin resistance than several others in a cross-sectional analysis among elderly Italians [14]. However, the independent association of C3 with the development of MetS has not been adequately studied to date.

Serum C3 was recently shown to be an independent predictor of type 2 diabetes mellitus in men. Engström et al [15] found that C3 levels related to risk of developing diabetes in more than 2700 healthy middle-aged men at a follow-up of 6.1 years. Complement C3 was the only marker among inflammation-sensitive plasma proteins that proved to be independent of body mass index, insulin, and other inflammatory markers.

We therefore explored prospectively among unselected 1220 men and women of a representative sample population having a high prevalence of the MetS [16] (*a*) whether C3 was a predictor of newly developed MetS, type 2 diabetes mellitus, and CHD independent of obesity and/or other inflammatory markers; (*b*) whether CHD risk is conferred by C3 additive to that of MetS; and (*c*) whether elevated C3 may be part of the cluster of MetS.

2. Population and methods

2.1. Subjects

The study sample of unselected participants of the Turkish Adult Risk Factor study [17] is formed by 1428 participants in whom serum complement C3 was measured in the survey of 2003/2004. After excluding 14.6% of those who subsequently were not tracked, the remaining 1220 subjects constituted the study sample. A previous cross-sectional report was confined to participants surveyed in 2003 alone [4], constituting half of the current sample. Participants were of 35 to 80 years of age at baseline and residents in each geographic region of Turkey. The study was approved by the Ethics Committee of the Istanbul University Medical Faculty. Written informed consent was obtained from all participants.

Waist circumference was measured with the subject standing and wearing only underwear, at the end of gentle expiration at the level midway between the lower rib margin and the iliac crest. Status of cigarette smoking status was categorized into current smokers, former smokers, and never smokers. Anyone who drank once a week or more frequently was considered as user of alcoholic drinks. Blood pressure (BP) was measured in the seated position on the right arm using an aneroid sphygmomanometer (Erka, Bad Tölz, Germany) after at least 5 minutes of rest, and the mean of 2 recordings 3 minutes apart was computed. Participants categorized themselves at baseline into 5 predefined increasing family income brackets, and physical activity was graded by the participants themselves into 4 categories of increasing order with the aid of a scheme [17]. Blood samples were collected in an 11-hour or longer fasting state in 93% of individuals in this study. Samples were shipped on cooled gel packs to Istanbul to be stored in deep freeze at −75°C until analyzed at the Yıldız Technical University. Serum concentrations of C3c and C-reactive protein (CRP) were measured by Behring kits and nephelometry (BN Prospec; Behring Diagnostics, Westwood, MA). Calibrators and controls (N/T Protein Control SL/M and N/T Rheumatology Control SL-1), supplied by the manufacturer (Behring Diagnostics), were used for each batch of measurement. Interassay coefficient of variation for C3c control was 2.1%, and intraassay coefficient of variation was 2.4%. Concentrations of insulin were determined by the chemiluminescent immunometric method using Roche kits (Roche Diagnostics, Mannheim, Germany) and Elecsys 1010 immunautoanalyzer.

Serum concentrations of total cholesterol, fasting triglycerides, glucose, and high-density lipoprotein cholesterol (HDL-C) (directly without precipitation) were determined by using enzymatic kits from Roche Diagnostics with a Hitachi 902 autoanalyzer. Low-density lipoprotein cholesterol values were computed according to the Friedewald formula. Serum apolipoprotein (apo) A-I and B values were measured by the nephelometric method (Behring), whereas fibrinogen levels were assayed in plasma, collected in sodium citrate–containing Vacutainers (Greiner Bio-One, Kremsmünster, Austria), by the modified Clauss method using Behring Fibrintimer II coagulometer and Multifibren U kit.

2.2. Definitions and outcomes

Individuals with diabetes were diagnosed with the criteria of the American Diabetes Association [18], namely, when plasma fasting glucose was at least 126 mg/dL (or 2-hour postprandial glucose >200 mg/dL) and/or the current use of diabetes medication as self-reported. Individuals with MetS were identified when 3 out of the 5 criteria of the National Cholesterol Education Program (Adult Treatment Panel III) [13] were met, modified for prediabetes (fasting glucose 100-125 mg/dL [19]) and further for abdominal obesity using as cut point of at least 95 cm in men, as recently assessed in the Turkish Adult Risk Factor study [20]. Missing data on triglycerides in one eighths of the sample did not preclude the identification of MetS because the MetS status of a previous or subsequent survey was adopted in few individuals presenting 2 positive criteria.

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 electrocardiogram [21], or a history of myocardial revascularization. Typical angina and, in women, age more than 45 years were prerequisite for a diagnosis when angina was isolated. Electrocardiographic 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. Coronary heart disease death comprised fatal coronary event and death from heart failure of coronary origin.

2.3. Exclusion and follow-up

The cohort included 92 patients with prevalent CHD, 365 with MetS, and 111 with type 2 diabetes mellitus at baseline, each of whom were excluded in the respective analyses. Participants were tracked from over a maximum of 4 years (mean, 3.3 years).

2.4. Data analysis

Descriptive parameters were shown as means ± SD or in percentages. Because of skewed distribution, values derived from log-transformed (geometric) means were used for serum triglycerides, CRP, γ-glutamyl transferase (GGT), insulin, and homeostasis model assessment (HOMA) index. Two-sided t tests and Pearson χ^2 tests served to analyze the differences in means and proportions between groups. Linear regression analyses were made in models with complement C3 as dependent variable for its covariates. Serum complement C3 was used as a continuous variable and, in regard to MetS, as quartiles for logistic regression analyses to ascertain whether or not a threshold effect existed. The quartiles were formed using cut points 1.12, 1.28, and 1.48 g/L. In predicting outcomes from baseline examination, Cox proportional hazards regression was used to yield risk coefficients (and 95% confidence intervals [CIs]) for each risk variable in models that controlled for potential confounders, after exclusion of participants with the outcomes sought at baseline examination. Relative risks (RRs) were expressed in terms of increments of 1 SD of complement C3 (0.27 g/L) or of other variables. A value of $P < .05$ on the 2-sided test was considered statistically significant. Statistical analyses were performed using SPSS-10 for Windows (SPSS, Chicago, IL, no. 9026510).

3. Results

The distribution of complement C3 values in 1220 individuals (534 men, 686 women) ranged from 0.6 to 2.2 g/L and was substantially normal, with skewness being 0.66 ($P = .08$) and kurtosis being 1.4 ($P = .16$). Variance of C3 values consisted of 0.074 g/L. Mean concentrations, 1.30 ± 0.27 g/L, did not differ significantly between men and women: 1.28 ± 0.27 and 1.32 ± 0.28 g/L, respectively. Mean C3 values in nonfasting subjects were only 1.2% higher than those in fasting participants. Total follow-up amounted to 4030 person-years (mean, 3.3 ± 0.9 years), during which 88 men and women developed incident fatal or nonfatal CHD (23.6 per 1000 person-years), after exclusion of the prevalent cases of CHD.

Table 1
Characteristics of sample population (N = 1220) at baseline by sex

	N	Men (n = 534)		Women (n = 686)		$P<$
		Mean	SD	Mean	SD	
Age, y	1220	52.6	10.6	52.4	10.4	NS
Menopause, n %		-	-	364	53	
Body mass index, kg/m^2	1220	28.0	5.0	30.5	5.5	†
Waist circumference, cm	1217	95.7	10.7	94.1	12	*
Systolic BP, mm Hg	1216	124.4	20.5	130.9	23	†
Diastolic BP, mm Hg	1216	79.6	10.8	82.1	11.9	†
Complement C3, g/L	1220	1.28	0.27	1.32	0.28	NS
Plasma fibrinogen, g/L	928	3.02	0.96	3.32	0.94	†
CRP[a], mg/L	1177	2.01	3.23	2.41	3.12	*
Apo A-I, g/L	884	1.31	0.26	1.43	0.30	†
Fasting insulin[a], mIU/L	1074	7.93	2.02	8.34	1.88	NS
Total cholesterol, mmol/L	1205	4.9	1.0	5.23	1.1	†
HDL-C, mmol/L	1219	1.02	0.29	1.23	0.32	†
LDL cholesterol, mmol/L	1028	2.9	0.85	3.16	0.96	†
Fasting triglycerides, mmol/L	1030	2.20	1.4	1.83	1.00	†
Fasting glucose, mmol/L	1095	5.82	2.2	5.52	2.2	*
HOMA[a] index	1067	1.84	2.2	1.90	2.12	.52
GGT[a], U/L	1159	26.4	1.85	19.6	1.88	†
Physical activity grade, 1-4	1215	2.5	1.0	2.1	0.8	†
Family income bracket, 1-5	1220	2.8	1.1	2.5	1.2	*
Current/former smoker, n	1220	233/142		91/19		†
Alcohol use, n %	1220	79	14.8	3	0.4	†

LDL indicates low-density lipoprotein; NS, not significant.
[a] Mean ± SD denotes values derived from log-transformed means and SD.
* $P < .05$ between sexes.
† $P < .001$ between sexes.

Clinical characteristics of the sample population (mean age, 53 ± 10.5 years) are shown in Table 1 separately for men and women. Men had lower BP, HDL-C, apo A-I, and plasma fibrinogen but higher triglycerides than women and were more frequently current smokers and users of alcoholic drinks. Lipid-lowering drugs were reported by 2.5% of participants; hormone replacement therapy, none.

3.1. Relationship of C3 with other risk parameters

In multiple linear regression models comprising 12 variables, associations for serum C3 were tested among men and women separately with age, waist girth, fasting glucose and triglycerides, HDL-C, CRP, GGT, systolic BP, physical activity grade, alcohol use, smoking status, and, in women, menopausal status (Table 2). In each sex, C3 was associated independently foremost with serum triglycerides and significantly with waist circumference, CRP, and, in men, inversely, with alcohol use. In combined sexes, C3 was reduced in current vs never smokers ($\beta = -0.07 \pm 0.02$, $P < .001$) and was associated with GGT ($\beta = 1.024 \pm 1.013$, $P = .054$). Aging was not independently associated with C3, although a slight inverse trend was apparent. When HOMA index was entered into this model, a 2-fold rise in HOMA was associated with a 2% decline in men ($P = .19$) and with a 3% rise in women ($P = .13$).

Table 2
Multiple linear regression analysis for covariates of complement C3 in men and women at baseline

	Men (n = 399)			Women (n = 553)		
	β coefficient	SE	P	β coefficient	SE	P
Fasting triglycerides[a], 0.6-fold	**1.91**	1.11	<.001	**2.30**	1.13	<.001
CRP[a], 3-fold	**1.058**	1.01	<.001	**1.069**	1.015	<.001
Waist circumference, 11 cm	**0.072**	0.011	<.001	**0.046**	0.011	<.001
Alcohol use, yes/no	**−0.070**	0.03	.024	−0.061	0.13	.65
Current, former, never smoker	*−0.043*	0.026	.087	*−0.053*	0.03	.081
GGT[a], 2-fold	1.015	1.02	.44	1.020	1.017	.25
HDL-C, 12 mg/dL	−0.008	0.012	.48	0.010	0.012	.35
Fasting glucose, 20 mg/dL	0.0008	0.001	.88	0.0012	0.001	.84
Menopause, yes/no				0.056	0.036	.12
Complement C3 variance	r^2 = 0.47, P = < .001			r^2 = 0.39, P < .001		

Units after each variable denote 1 SD. Model adjusted also for age, systolic BP, and physical activity grade (all Ps > .18). Significant values are highlighted in bold.
[a] Log-transformed values.

3.2. Independent risk conferred for MetS and CHD by complement C3

In a logistic regression model, after adjustment for sex, age, smoking status, GGT, CRP, physical activity grade, and alcohol use, the highest C3 quartile predicted MetS with RRs of 3.69 (95% CI, 1.54-8.86) in 295 men and 5.98 (95% CI, 2.47-14.5) in 311 women free of MetS. Even quartile 2 in women exhibited an RR of 3.00 (95% CI, 1.38-6.52). When in Cox regression analysis all 5 components of MetS, smoking status, family income, lipid-lowering drug, and, in women, menopausal status substituted physical activity grade and alcohol use in the previous model (Table 3, upper panel), increasing C3 quartiles persisted to predict strongly MetS in women and in both sexes combined. Significance was lost in men even in the highest quartile.

Areas under the receiver operating curve for prediction of CHD for C3 concentrations were 0.58 (0.49-0.67) in men and 0.64 (0.56-0.73) in women. Relative risk of C3 for incident CHD risk adjusted for sex, age, and the presence of MetS proved to be significant with 1.42 (95% CI, 1.13-1.78) for an increment of 1 SD in combined sexes. It was 1.41 (95% CI, 1.00-1.99) among 488 men and 1.45 (95% CI, 1.07-1.95) in 640 women. After further adjustment for

Table 3
Cox regression analysis for predicting incident MetS and CHD by baseline complement C3 quartiles or concentrations

MetS	RR	95% CI	RR	95% CI	RR	95% CI
	Total (n = 137/495)[b]		Men (n = 63/230)		Women (n = 74/265)	
C3 Q2, 1.12-1.28 g/L	**1.74**	1.06; 2.57	1.15	0.56; 2.25	**2.53**	1.24; 5.16
C3 Q3, 1.28-1.47 g/L	**2.23**	1.33; 3.49	1.42	0.68; 2.97	**3.30**	1.53; 7.12
C3 Q4, ≥1.48 g/L	**2.27**	1.29; 4.01	2.00	0.88; 4.51	**3.16**	1.39; 7.20
GGT[a], 2-fold	*1.12*	0.98; 1.26	**1.27**	1.05; 1.53	0.98	0.82; 1.18
CRP[a], 3-fold	0.95	0.84; 1.06	1.08	0.91; 1.28	**0.84**	0.71; 1.00
Current smoking, 2/0	0.75	0.47; 1.21	0.84	0.45; 1.60	0.63	0.28; 1.43
Abdominal obesity	**2.93**	1.88; 4.55	**3.05**	1.62; 5.73	**3.08**	1.61; 5.87
Elevated BP	**2.44**	1.52; 3.93	**2.28**	1.10; 4.72	**3.02**	1.54; 5.95

Model adjusted also for sex, age, lipid-lowering drug use, family income, and, in women, menopause (all not significant) and the remaining 3 MetS components (P < .002 in all).

CHD

	n = 84/1061[c]		n = 41/467		n = 43/594	
Sex, female	0.90	0.55; 1.69				
Age, decade	**1.79**	1.44; 2.24	**2. 60**	1.49; 2.84	*1.61*	0.99; 2.62
MetS, yes/no	1.44	0.88; 2.35	1.29	0.65; 2.58	1.40	0.68; 2.89
Complement C3, 0.27 g/L	**1.35**	1.09; 1.67	1.**46**	1.06; 2.02	*1.32*	0.98; 1.79
Current smoking, 2/0	*1.79*	0.95; 3.40	1.72	0.76; 3.88	2.54	0.76; 8.49
CRP[a], 3-fold	1.09	0.95; 1.25	1.05	0.87; 1.26	1.13	0.91; 1.39

Model adjusted also for lipid-lowering drug use (P = .93 in women, P < .012 in men and total), family income, and, in women, menopause (P > .3 in both).
[a] Log-transformed values.
[b] Number of new MetS/number at risk in model.
[c] Number of new CHD/number at risk in model.

smoking status, CRP, lipid-lowering drug use, family income, and menopause (Table 3, lower panel), the RR of C3 in combined sexes attenuated only to 1.35 (95% CI, 1.09-1.67) for 1-SD increment of C3. Relative risks were 1.46 (95% CI, 1.06-2.02) in men and 1.32 (P = .068) in women. The 2 log likelihood in the models for the difference of inclusion of C3 was 6.95 in the total sample (P = .01), 4.94 in men (P < .02), and 3.06 in women (P < .05).

3.3. C3, a determinant of diabetes in women, not men

Serum C3 was tested both for incident and combined prevalent and incident type 2 diabetes mellitus (because of its new development of only 75 instances) in models adjusted for sex, age, and presence of MetS. In the larger model, adjustment for smoking status, lipid-lowering drug use, family income, and menopause was also made. Complement C3 was clearly not associated with diabetes independently in men in either model (Table 4). In women, however, C3 tended to contribute, additively to MetS, to the association with incident diabetes with similar RRs.

4. Discussion

In this population-based prospective study on middle-aged and elderly men and women, serum levels of complement C3 were associated significantly and independently with serum triglycerides, waist circumference, and CRP and, inversely, with smoking status and, in men, with alcohol use. Using Cox regression analyses, C3 levels were first shown in this study to predict future development of both MetS and CHD, independent of and additive to MetS components and CRP. Strength of the association in terms of 1-SD increment in C3 was 1.45 for MetS and 1.35 for CHD. Risk of type 2 diabetes mellitus was independently associated at a borderline significance with C3 in women alone.

4.1. Associations of C3

The linear regression model that accounted for a large variance in circulating C3 showed that fasting triglycerides, waist circumference, and CRP were the important independent covariates in our sample, each accounting for a mean of 0.07 to 0.1 g/L of the variation. In addition, current smoking and, in men, alcohol use were significantly associated with lower C3 values. Complement C3, as distinct from acylation stimulating protein and adiponectin, was found to be correlated with HOMA-defined insulin resistance in lean vs obese subjects with and without diabetes [22]. Evidence was reported by Muscari et al [14] that the association of C3 with insulin resistance was not mainly mediated by indices of obesity, with which our finding of HOMA being—mediated by other variables—not an independent determinant of C3 diverges. They also found that hepatic steatosis, a marker of abdominal obesity, was independently associated with insulin resistance. γ-Glutamyl transferase rather than C3 appeared to be an independent determinant of MetS in male subjects, whereas C3 seemed to contribute to the development of MetS in female subjects. Conceiveably, in the development of MetS, oxidative stress and vascular inflammation have different weighting and act separately in Turkish men and women, in whom dysfunctionalities of protective serum proteins are pronounced compared with men [23].

Of interest was the observation that both current smoking and alcohol use were associated with lower circulating C3 (by about 7%), independent of waist girth and other confounders. This is in line with an inverse linear association of current smoking and C3 with serum apo C-III among Turks [24] and may be related to the effect of smoking

Table 4
Logistic regression analysis of complement C3 concentrations for prevalent and incident diabetes and Cox regression analysis for incident diabetes

Prevalent and incident diabetes	RR	95% CI	RR	95% CI	RR	95% CI
	Total (n = 182/1193)[a]		Men (n = 93/529)		Women (n = 89/664)	
Sex, female	**0.62**	0.41; 0.94				
Age, decade	**1.34**	1.14; 1.61	**1.52**	1.21; 1.93	0.82	0.54; 1.23
MetS, yes/no	**3.52**	2.40; 5.17	**3.12**	1.86; 5.23	**4.60**	2.50; 8.46
Complement C3, 0.27 g/L	1.12	0.94; 1.33	0.98	0.75; 1.27	*1.25*	0.99; 1.59
Current smoking, 2/0	0.95	0.59; 1.53	0.92	0.51; 1.67	1.27	0.59; 2.72

Adjusted also for family income, lipid-lowering drug use, and, in women, menopause (P > .2 in all).

Incident diabetes	Total (n = 75/1086)[a]		Men (n = 45/481)		Women (n = 30/605)	
Sex, female	**0.49**	0.27; 0.88				
Age, decade	*1.21*	0.96; 1.54	**1.33**	1.01; 1.77	1.08	0.57; 2.06
MetS, yes/no	**1.92**	1.14; 3.24	**2.46**	1.29; 4.68	1.31	0.58; 2.94
Complement C3, 0.27 g/L	1.14	0.89; 1.46	1.05	0.76; 1.44	*1.36*	0.96; 1.94
Current smoking, 2/0	1.30	0.69; 2.48	1.11	0.53; 2.30	2.32	0.88; 6.12

Model adjusted also for family income, lipid-lowering drug use, and, in women, menopause (P < .2 in all).

[a] Number of new diabetes/number at risk in model.

protecting Turkish adults, particularly women, against MetS and type 2 diabetes mellitus [25].

4.2. Complement C3 and MetS risk

We demonstrated for the first time that circulating C3 strongly predicts the cluster of (Adult Treatment Panel III–defined) MetS independent of and additive to the MetS components. In partial agreement with this is a study on 490 subjects in which plasma C3 levels were found to be independently associated with MetS in South Asians but not in white people in whom CRP and plasminogen activator inhibitor-1 were so [26]. Previously, in a study of the covariates of MetS components in 1603 Chinese children and adolescents who comprised overweight/obese individuals, acylation-stimulating protein, but not complement C3, was reported to be associated with these components [27].

The strength of the association was remarkable matching from the third quartile of abdominal obesity in women. The stronger association than that in men might be due to serum C3 mediating the influence of GGT in women, whereas these 2 factors are independently related to MetS in Turkish men.

4.3. Complement C3 and CHD risk

Circulating C3 emerged also as an independent risk factor for future CHD risk that, as novelty, proved to be additive to that conferred by MetS. The strength of the independent association was similar in both sexes, with an RR of 1.35 for an increment of 0.27 g/L (=1 SD). That this was even independent of and superior to CRP levels, an established inflammatory marker and a determinant of cardiometabolic risk among Turks [28], is to be noted. A similar experience with these inflammatory markers was reported by Ajjan et al [29] in a cross-sectional case-control analysis.

Engström and coworkers [8] recently reported age-adjusted C3 to identify the prediction of coronary or cardiovascular events in 5850 middle-aged Swedish men at an 18-year follow-up. The association was weaker than that obtained in the present study and disappeared after adjustment for established risk factors. On the other hand, the C3/C4 ratio was found to be of predictive value for a composite end point of recurrent cardiovascular events in 148 Finnish patients with acute coronary syndrome followed -up over 1.5 years [9]. The OR was 1.33 (95% CI, 1.08-1.63) after adjustment for traditional risk factors and other confounders, an odds very close to that observed in the current study. Thus, it appears that serum C3 is an important independent risk factor for the development of CHD in the population at large as well as in patients with an acute CHD event.

4.4. Role of sex in risk of diabetes

Serum C3 was recently found to be an independent predictor of diabetes in middle-aged Swedish men [15], as pointed out above. We detected no contribution of circulating C3 to risk of diabetes to that of MetS in men, which implies that C3 levels may confer risk for developing MetS that in turn mediates the risk for diabetes in men. In contrast, in women, a modest, borderline-significant diabetes risk is additively imparted by C3 concentrations, like the greater MetS risk conferred in Turkish women than in men. This may be related to existence of more marked dysfunctions of HDL [23] and its apo A-I [30], A-II, and C-III [24] compared with men.

4.5. Collective assessment of C3 as a risk factor

Our findings in women suggest that elevated C3 concentrations are not only a prominent determinant of MetS but contribute independently to the risks of diabetes and CHD; thus, C3 appears to be part of the proinflammatory/oxidative state that is of great relevance to the mechanism of cardiometabolic disorders among Turkish women. Complement C3 has a commensurately smaller influence in men in whom insulin resistance assumes a greater role in the pathogenesis of MetS and diabetes; nonetheless, it confers substantial risk for CHD, independent of MetS itself.

Complement C3 is highly significantly and linearly related to apo C-III in the cohort of the Turkish Adult Risk Factor study, particularly its fraction on apo B–containing lipoproteins in women [24]. We hypothesize that the higher risk of MetS and diabetes observed in women may be ascribed to the enhancement of C3 by apo C-III and to the apo C-III fraction on HDL, a major diabetogenic factor in women [24]. Conceiveably, greater role of vascular inflammation and cellular adhesion molecules in women may underlie this sex difference.

Our finding that mean C3 values in subjects were not significantly higher than those in fasting participants suggests that fasting status is not a salient confounding factor and that, if at all, relation to cardiometabolic risk may have been slightly weakened because of a dilution effect. Some caution may be in place for applicability of the herein-reached conclusions to populations that do not have a high prevalence of adiposity or cardiometabolic disorders, yet broadly similar influence on CHD risk was reported among Scandinavians. Strengths of the current study include prospective design; a relatively large cohort of both sexes representative of a middle-aged general population; availability of adjustments for MetS and other relevant confounders; combined assessment in 1 study of the risk for MetS, diabetes, and CHD; and a high prevalence of cardiometabolic risk among Turks studied.

In conclusion, C3 concentrations are associated independently and linearly with waist circumference, serum fasting triglycerides, and CRP, and inversely with the smoking habit. Levels of C3 predict strongly incident MetS independent of and additive to its components as well as of CRP and GGT and thus constitute part of the syndrome cluster. The C3 levels predict CHD in both sexes, even independently of age, smoking status, family income, CRP,

and the presence of MetS. The C3 levels contribute to the risk of type 2 diabetes mellitus only in women.

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