Association Between C-Reactive Protein and Features of the Metabolic Syndrome

A population-based study

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OBJECTIVE — To assess the association of circulating levels of C-reactive protein, a sensitive systemic marker of inflammation, with different components of the metabolic syndrome.

RESEARCH DESIGN AND METHODS — Total cholesterol (TC), HDL cholesterol, triglycerides, uric acid, BMI , and prevalence of diabetes and hypertension were assessed in 747 men and 956 women aged 18–89 years who were participating in the population-based National Health and Nutrition Survey, which was carried out in former West Germany in 1987–1988.

RESULTS — There was a statistically significant positive crude correlation between C-reactive protein and TC ($R = 0.19$), TG ($R = 0.29$), BMI ($R = 0.32$), glucose ($R = 0.11$), and uric acid ($R = 0.14$) (all $P < 0.0001$). A negative correlation was found between C-reactive protein and HDL cholesterol ($R = 0.13$, $P < 0.0001$). The age-adjusted geometric means of C-reactive protein concentrations in subjects grouped according to the presence of 0–1, 2–3, and ≥4 features of the metabolic syndrome were 1.11, 1.27, and 2.16 mg/l, respectively, with a statistically highly significant trend ($P < 0.0001$).

CONCLUSIONS — The data suggest that a variety of features of the metabolic syndrome are associated with a systemic inflammatory response.

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The metabolic syndrome (MS) is characterized by insulin resistance accompanied by one or more of the following: obesity, hypertension, impaired glucose tolerance, low HDL cholesterol levels, and/or hypertriglyceridemia (1–3). In the San Antonio Heart Study (1), only 36% of the subjects were free of all six disorders, indicating that the MS is very common. Moreover, there is much evidence that the MS is associated with a greatly increased risk of coronary heart disease (CHD) (4,5).

Although both hereditary (6,7) and environmental factors contribute to the development of the MS, little is known about the underlying pathogenetic mechanisms. However, a central role has been attributed to the proinflammatory cytokines tumor necrosis factor-α (TNF-α) (8) and interleukin (IL)-6 (9), supported by the fact that both are produced in substantial amounts by human adipose tissue. TNF-α impairs insulin-stimulated glucose uptake in a variety of cells and decreases lipoprotein lipase activity. Both cytokines increase hepatic lipogenesis (10,11) and elicit a systemic acute-phase response (12). Furthermore, various aspects of the acute-phase response, such as fibrinogen (13) and plasminogen activator inhibitor 1 levels (14,15), whole-blood viscosity (16), and white blood cell count (17), have recently been found to correlate positively with the MS. This is of particular interest because inflammation plays an important role in the pathogenesis of atherothrombosis (18,19). Macrophage and T-cell infiltration is a major feature of atherosclerotic plaques (20), especially at sites of plaque rupture, and epidemiological studies show strong positive associations of systemic markers of inflammation with atherothrombotic disease (14,21–23). Moreover, C-reactive protein (CRP), the classic and exquisitely sensitive acute-phase reactant, shows a strong independent association with risk of CHD and other atherothrombotic events (24–28). CRP levels have also been found to correlate with BMI and some other features of the MS (24,28–31). Therefore, the aim of the present study was to systematically investigate the association of CRP with components of the MS in a large population-based sample.

RESEARCH DESIGN AND METHODS

Study population

A multistage stratified probability sample comprising 2,006 men and women was recruited, with a participation rate of ~70%, as part of the National Health and Nutrition Survey conducted among apparently healthy noninstitutionalized people aged 18–89 years in West Germany in 1987–1988 (VERA Study) [Verbundstudie Ernährungserhebung und Risikofaktoren Analytik] (32). Subjects with acute illnesses were excluded from the study, but people with a history of chronic disease, such as ischemic heart disease, diabetes, or cancer, were not excluded. There were

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Abbreviations: CHD, coronary heart disease; CRP, C-reactive protein; IL, interleukin; MS, metabolic syndrome; MONICA, ; TC, total cholesterol; TG, triglycerides; TNF-α, tumor necrosis factor-α.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Distribution of variables*

Variable	Mean	SD	Median	5th percentile	95th percentile
Age (years)	43.5	15.7	42	21	69
CRP (mg/l)	3.15	7.40	1.07	0.21	9.35
BMI (kg/m^2)	25.0	4.2	24.6	19.2	32.5
TC (mmol/l)	5.52	1.31	5.40	3.78	7.60
HDL (mmol/l)	1.15	0.29	1.11	0.75	1.66
TG (mmol/l)	1.29	0.94	1.05	0.51	2.86
Glucose (mmol/l)	5.35	1.19	5.16	4.39	6.60
Uric acid (μmol/l)	296.3	77.5	289.0	186.0	435.0

only minor differences in age and sex distribution between the study sample and the target population.

Data collection

A standardized interview was conducted by trained personnel; detailed information was collected on medical history, dietary habits, and lifestyle characteristics, including smoking, alcohol consumption, and physical activity. BMI was computed, and fasting venous blood samples were drawn from 1,834 subjects (91%) with short-term venous occlusion and minimal suction.

Laboratory analyses

All blood analyses were performed in a central laboratory. Triglycerides (TG) and total cholesterol (TC) were determined enzymatically (LKB substrate analyzer/diluter; Boehringer Mannheim, Mannheim, Germany). After microultracentrifugation (d = 1,006 kg/l, 3 h at 4°C), HDL cholesterol was detected in the supernatant. Serum glucose was determined by a glucose dehydrogenase method. Uric acid was measured photometrically after incubation with uricase and a color reagent (Technicon Instruments, Tarrytown, NY). Serum samples were stored in liquid nitrogen at −130°C, and CRP concentration was measured, as previously reported (28), by an immunoradiometric assay (range 0.05–10 mg/l) calibrated with the World Health Organization reference standard 85/506 (33). Coefficient of variation for repeated measurements of CRP was 12% over all ranges.

Statistical analyses

The current analysis is restricted to 1,703 subjects with complete data on all features of the MS and CRP. Characteristics of the MS were defined by the following cutoff limits (34): BMI ≥26 kg/m^2 for women and ≥27 kg/m^2 for men, TC ≥5.2 mmol/l, HDL cholesterol <0.9 mmol/l for men and <1.1 mmol/l for women, TG ≥1.7 mmol/l, and uric acid ≥400 μmol/l. Prevalence of diabetes was assessed either by fasting blood glucose levels ≥7.0 mmol/l (35) and/or the reported presence of diabetes and/or treatment with antidiabetic drugs. Subjects were considered to be hypertensive if they had a reported diagnosis of hypertension and/or treatment with antihypertensive drugs. CRP values were highly skewed and were normalized by logarithmic transformation in all analyses. Values of other variables were close to normally distributed and were therefore not transformed. Additional statistical analyses were done excluding individuals with CRP levels >10 mg/l, indicating clinically relevant inflammatory conditions, but this did not alter our results. Spearman's correlation analyses were performed between values for CRP and components of the MS. Geometric mean values of CRP were calculated across categorized features of the MS. All mean values were adjusted for sex, age (years), smoking status (current, former, or never), and the remaining features of the MS (BMI [kg/m^2], TC [mmol/l], HDL cholesterol [mmol/l], TG [mmol/l], glucose [mmol/l], uric acid [mmol/l], and hypertension [yes/no]) by means of a multiple general linear regression model (Procedure for General Linear Regression Models in SAS). Subjects with a different number of features of the MS were grouped as follows: cluster I for 0–1 features, cluster II for 2–3 features, and cluster III for 4–7 features. Age-adjusted geometric means of CRP were then calculated for each cluster. All tests were performed at a nominal 5% level and were computed using SAS software, version 6.12 for Windows.

RESULTS — The distribution of components of the MS in the study population is shown in Table 1. Spearman's rank correlation coefficients between CRP and variables of the MS are shown in Table 2. There was a statistically significant unadjusted positive correlation ($P < 0.0001$) between CRP and age, BMI, TC, TG, fasting glucose, and uric acid, and a significant negative correlation of CRP with HDL cholesterol ($P < 0.0001$). The strongest correlation ($r = 0.32$) was observed between CRP and BMI. The adjusted geometric means of CRP for categorized features of the MS are shown in Table 3. The cutoff points used are in accordance with recommendations of an international body of experts (34,35). There was a high prevalence of overweight subjects (41.3%), hypertensive subjects (20.2%), and subjects with diabetes (4.5%). The means were statistically highly significantly different in categories of BMI ($P < 0.0001$), with higher CRP values in subjects with a BMI >26 kg/m^2 in women and >27 kg/m^2 in men. This is in accordance with the strong positive correlation of BMI and CRP seen in Spearman's rank correlation. There was also a significant difference in means of CRP between categories of diabetes and uric acid. Although means of CRP differed among categories of TC, HDL cholesterol, TG, and hypertension, they were not statistically significant because of a wide scattering of values.

More than one component of the MS was present in most individuals; therefore, we analyzed CRP values in groups with different numbers of features, as follows: category I, no MS feature (0–1 feature); category II, moderate MS (2–3 features); category III, severe MS (4–7 features) (Table 4). Most subjects were in category II, indicating that moderate MS is quite common in the population. There was an appreciable number of individuals with severe MS, and 1.1% of the total population subjects had more than five features of the MS. The results show a positive and statistically highly significant trend in CRP levels with an increasing number of features of the MS.

Table 2—*Spearman rank correlations between CRP and variables of the MS*

Variable	CRP	*P*
Age	0.20	<0.0001
BMI (kg/m^2)	0.32	<0.0001
TC (mmol/l)	0.19	<0.0001
HDL (mmol/l)	−0.13	<0.0001
TG (mmol/l)	0.29	<0.0001
Glucose (mmol/l)	0.11	<0.0001
Uric acid (μmol/l)	0.14	<0.0001

Table 3—*Adjusted geometric means of CRP for categorized features of the MS*

Variable	*n*	Mean of CRP* (95% CI)	*P*†
BMI (kg/m^2)			
<26 for women/<27 for men	999	1.14 (1.03–1.27)	0.0001
≥26 for women/≥27 for men	704	1.76 (1.56–1.97)	—
TC (mmol/l)			
<5.2	721	1.35 (1.20–1.51)	0.72
≥5.2	982	1.38 (1.24–1.53)	—
HDL (mmol/l)			
≥0.9 for men/≥1.1 for women	1,012	1.31 (1.19–1.44)	0.11
<0.9 for men/<1.1 for women	691	1.46 (1.29–1.63)	—
TG			
<1.7 mmol/l	1,376	1.39 (1.26–1.51)	0.67
≥1.7	327	1.33 (1.13–1.56)	—
Diabetes			
No (fasting blood glucose <7.0 mmol/l)	1,628	1.34 (1.22–1.46)	0.005
Yes (fasting blood glucose ≥7.0 mmol/l)	75	2.03 (1.52–2.69)	—
Uric acid (μmol/l)			
<400	1,550	1.35 (1.23–1.48)	0.01
≥400	153	1.77 (1.44–2.02)	—
Hypertension			
No	1,359	1.30 (1.20–1.41)	0.21
Yes	344	1.43 (1.24–1.66)	—

*Adjusted for age, smoking, and all other features; †difference of the means.

CONCLUSIONS — We report a positive correlation between serum CRP concentration and the MS in a large population-based sample. Adjusted values revealed a statistically significant association between CRP and BMI, diabetes, and uric acid. The strongest association of CRP was found with BMI. However, because the MS represents a cluster of simultaneously occurring features, it may not be appropriate to look only at isolated variables. Indeed, we found that CRP values clearly increase with the number of manifestations of the MS. CRP values were nearly twice as high in subjects with severe MS compared with those without it, and in the few individuals with a cluster of six or seven features of the MS, there was a threefold increase.

In a recently published analysis of the Oxford and Collaborators Health Check Study, in which individuals without a history of CHD were included (31), a significant association of CRP with obesity could be demonstrated, but no association was found with other components of the MS. The European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study (24) conducted among subjects with angina pectoris reported an increased CRP with both increases in BMI and TG, and the Cardiovascular Health Study (29), which included only elderly people, showed a significant positive correlation between CRP and BMI, TG, and uric acid, and a significant negative correlation with HDL cholesterol, as we found here. In an analysis from the population-based Monitoring Trends and Determinants in Cardiovascular Disease Study (28), which only included men 45–64 years of age, CRP increased significantly with BMI and blood pressure and decreased with HDL cholesterol. Subjects with diabetes had significantly higher CRP concentrations than nondiabetic individuals, and the relation of CRP to TC was U-shaped in unadjusted analyses, with higher CRP levels in individuals with very low and very high TC concentrations. This complex association of CRP with TC may explain the absence of a significant association with TC levels seen here. In contrast to the MONICA Study, CRP levels in categories of hypertension did not differ significantly in our study. This may be due to lack of precision when using only a standardized interview to assess hypertension.

Juhan-Vague et al. (15) demonstrated for the first time a significant linear increase of CRP levels with increasing insulin concentrations. This is in accordance with our finding of increasing CRP levels in relation to an increasing number of features characterizing the MS. The geometric mean of CRP in the highest quartile of insulin concentration was 2.08 mg/l, which is very similar to the mean CRP level of 2.16 mg/l found in subjects with severe MS (≥4 features). Another study conducted in diabetic patients with and without additional features of the MS (36) showed significantly elevated acute-phase reactants, including CRP and IL-6 in those subjects with MS. In a small group of 107 nondiabetic subjects, Yudkin et al. (37) demonstrated a strong relationship of the MS with acute-phase markers, including CRP, IL-6, TNF-α, and fibrinogen. This relationship was only slightly weakened after removing measures of obesity from the score, which led to the suggestion that cytokines might be responsible for all of the metabolic disorders associated with the MS.

IL-6 and TNF-α are both produced in appreciable amounts in adipose tissue, but only IL-6 is released from adipose tissue into the systemic circulation. Approximately 30% of total IL-6 production may arise in adipose tissue (9) and thus may be able to mediate both the systemic acute-phase response and the systemic metabolic impairments of the MS. In contrast, although TNF-α acts only locally in a paracrine manner, it may still contribute considerably to insulin resistance of adipocytes and muscle cells (11). The elevated CRP concentrations seen in the present study in subjects with severe MS may reflect cytokine production by adipocytes, because IL-6 levels and CRP concentrations are closely related in obese subjects (38). However, in addition to being another useful marker of insulin resistance, increased CRP levels may have significant

Table 4—*Adjusted geometric means of CRP for clustered features of the MS*

Numbers of features	*n*	CRP* (95% CI)
Group I	490	1.11 (0.97–1.26)
0	66	1.15 (0.84–1.55)
1	424	1.08 (0.94–1.24)
Group II	898	1.27 (1.16–1.40)
2	533	1.14 (1.01–1.28)
3	365	1.50 (1.31–1.73)
Group III	315	2.16 (1.86–2.51)
4	208	1.94 (1.62–2.32)
5	90	2.73 (2.09–3.56)
6	16	3.28 (1.82–5.91)
7	1	—

*Geometric mean adjusted for age, sex, and smoking status. $P < 0.0001$ for trends.

clinical implications. An increased CRP concentration is an independent risk factor for CHD (24–28), and there are several possible mechanisms by which CRP might be both proatherogenic and prothrombotic (39), including its interaction with LDL (40) and complement CRP complexes (41) and its capacity to stimulate tissue factor production by macrophages (42).

The present study is potentially limited by the fact that insulin resistance (43), the key component of the MS and the precursor of type 2 diabetes (44), was not determined directly by fasting insulin levels or by an oral glucose tolerance test. Insulin resistance is present in 15–30% of people in Western industrialized countries (45,46). In the present study, raised fasting blood glucose levels (>7.0 mmol/l), indicating apparent type 2 diabetes (35), were found in 4.5% of subjects, which is in accordance with previous epidemiological findings in West German populations (47). Because only subjects with overt diabetes were scored in our analysis, the observed correlations are most likely to be underestimates. A further concern may be that hypertension was assessed by a standardized interview and not by a sphygmomanometric measurement (6); however, the 20.2% prevalence we found is similar to that reported in other West German studies (48). Finally, our cross-sectional study design lacks information on the time sequence of events and, thus, does not permit identification of causal relationships. However, it has the admirable quality of being able to comprise a large population-based sample, while limiting the selection bias often encountered in clinical settings.

In summary, we found an association between the acute-phase marker CRP and a number of disorders characterizing the MS. We conclude that the MS is associated with a systemic inflammatory response, which plays an important pathogenetic role in atherothrombotic disease. This may represent a further mechanism for the increased CHD risk seen in these subjects.

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