

Roles of the Metabolic Syndrome, HDL Cholesterol, and Coronary Atherosclerosis in Subclinical Inflammation

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University of Innsbruck approved the study; all participants gave written informed consent.

OBJECTIVE— The metabolic syndrome (MetS) and coronary artery disease (CAD) frequently coincide; their individual contribution to inflammation is unknown.

RESEARCH DESIGN AND METHODS— We enrolled 1,010 patients undergoing coronary angiography. Coronary stenoses $\geq 50\%$ were considered significant. The MetS was defined according to American Heart Association–revised National Cholesterol Education Program Adult Treatment Panel III criteria.

RESULTS— C-reactive protein (CRP) did not differ between patients with significant CAD and subjects without significant CAD ($P = 0.706$) but was significantly higher in MetS patients than in those without MetS ($P < 0.001$). The MetS criteria low HDL cholesterol ($P < 0.001$), large waist ($P < 0.001$), high glucose ($P < 0.001$), and high blood pressure ($P = 0.016$), but not high triglycerides ($P = 0.352$), proved associated with CRP. When all MetS traits were considered simultaneously, only low HDL cholesterol proved independently associated with CRP ($F = 44.19$; $P < 0.001$).

CONCLUSIONS— CRP is strongly associated with the MetS but not with coronary atherosclerosis. The association of the MetS with subclinical inflammation is driven by the low HDL cholesterol feature.

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Although serum C-reactive protein (CRP) is an important predictor of cardiovascular events (1), its cross-sectional association with the presence and extent of coronary atherosclerosis is unclear (2,3). It is therefore ambiguous whether subclinical inflammation in metabolic syndrome (MetS) patients is primarily due to the increased prevalence of (silent) coronary artery disease (CAD) in these patients or, conversely, whether elevated levels of inflammation in CAD patients are primarily due to a correlation with the MetS. Furthermore, it remains unclear which classical MetS traits are most strongly associated with CRP.

RESEARCH DESIGN AND METHODS

We enrolled 1,047 consecutive Caucasian patients referred to coronary angiography for the evaluation of stable CAD solely on a clinical indication. Six patients with type 1 diabetes and 31 patients with acute infections were excluded.

Coronary angiography was performed as described previously (4); coronary stenoses $\geq 50\%$ were considered significant (5,6). The MetS was diagnosed according to American Heart Association–revised National Cholesterol Education Program Adult Treatment Panel III criteria (7). The ethics committee of the

Analytical procedures and statistical analyses

Analytical procedures were performed on a Cobas Integra 800 (Roche, Basel, Switzerland), as described previously (4,8). Sample-size calculations showed that assuming an SD of 1.5 times the population mean, 393 patients would be needed per study group to detect a between-group difference of CRP of 20% with a power of 80% at an α fault of 0.05. P values < 0.05 were considered significant. The Hochberg correction for multiple testing was applied where appropriate. Statistical analyses were performed with the software package SPSS 11.0 for Windows.

RESULTS

Association between the MetS and angiographically determined coronary atherosclerosis

Significant CAD at angiography was present in 564 patients (55.8%); its prevalence was higher in patients with MetS than in subjects without MetS (59.5 vs. 52.8%; $P = 0.034$); adjustment for age, sex, LDL cholesterol, smoking, cardiovascular medications (statins, aspirin, ACE inhibitors/angiotensin receptor blocking agents and β -blocking agents), and CRP confirmed this result, with an odds ratio (OR) of 1.49 (95% CI 1.12–1.98; $P = 0.007$) for MetS patients.

The low HDL cholesterol (OR 1.57 [95% CI 1.11–2.22]; $P = 0.011$) and the high-glucose traits (1.33 [1.02–1.73]; $P = 0.038$) proved significantly and independently of the above covariates associated with significant CAD, whereas high triglycerides ($P = 0.082$), large waist ($P = 0.826$), and high blood pressure criteria ($P = 0.145$) were not independently associated with significant CAD.

CRP, MetS, and CAD

CRP was significantly higher in patients with MetS than in subjects without MetS (0.46 ± 0.62 vs. 0.35 ± 0.49 mg/dl; $P < 0.001$). In contrast, CRP did not differ sig-

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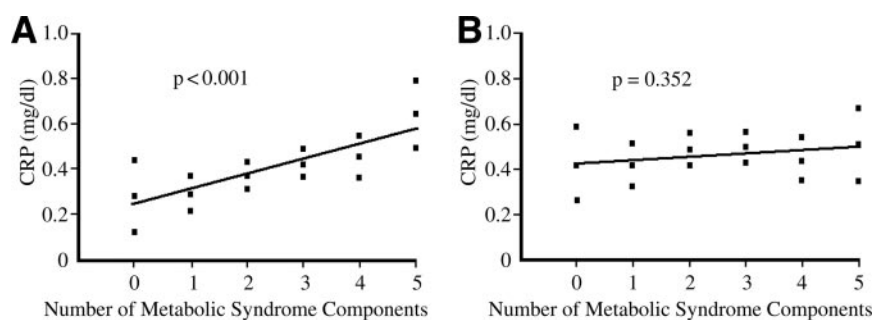


Figure 1—A: Relationship of the number of MetS components and CRP adjusted for age, sex, LDL cholesterol, smoking, and major cardiovascular medications. B: Further adjustment for the low HDL criterion. P value is given for the association of CRP with the number of MetS components.

nificantly between patients with significant CAD and subjects without significant CAD (0.40 ± 0.59 vs. 0.39 ± 0.52 mg/dl; $P = 0.706$). CRP also was similar in subjects with any atherosclerotic lesion at angiography compared with subjects with completely normal coronary arteries (0.41 ± 0.57 vs. 0.36 ± 0.50 mg/dl; $P = 0.325$). Furthermore, CRP was not associated with significant CAD in a multivariate model adjusting for age, sex, LDL cholesterol, smoking, cardiovascular medications, and presence of MetS (standardized adjusted OR 0.97 [95% CI 0.76–1.25]; $P = 0.822$).

Considering both MetS and significant CAD, CRP was significantly higher in patients with MetS, both among those without significant CAD (0.45 ± 0.50 vs. 0.36 ± 0.53 mg/dl; $P < 0.001$) and among those with significant CAD (0.47 ± 0.69 vs. 0.34 ± 0.45 ; $P = 0.001$). In contrast, CRP did not differ between patients with significant CAD and those without significant CAD among subjects without MetS ($P = 0.869$) or among subjects with MetS ($P = 0.411$).

ANCOVA, adjusting for age, sex, LDL cholesterol, smoking, and cardiovascular medications, confirmed that MetS ($F = 11.74$; $P = 0.001$) but not significant CAD ($F = 0.01$; $P = 0.983$) was significantly associated with CRP.

Associations of individual MetS components with CRP

Univariately, serum CRP was significantly higher in patients who fulfilled the large waist ($P < 0.001$), the low HDL cholesterol ($P < 0.001$), the high blood pressure ($P = 0.016$), and the high glucose ($P < 0.001$) criteria but not in patients who fulfilled the high triglyceride criterion ($P = 0.352$) compared with patients who did not fulfill the respective MetS criteria. When all MetS traits were entered simul-

taneously into one ANCOVA model, only low HDL cholesterol proved associated with CRP ($F = 44.19$; $P < 0.001$) independently of age, sex, LDL cholesterol, smoking, major cardiovascular medications, and of all other MetS criteria.

CRP increased significantly ($P_{\text{trend}} < 0.001$) with an increasing number of MetS traits (Fig. 1A) after adjustment for age, sex, smoking, LDL cholesterol, and major cardiovascular medications. Further adjustment for the high waist ($F = 11.66$; $P = 0.001$), the high glucose ($F = 14.18$; $P < 0.001$), the high blood pressure ($F = 17.94$; $P < 0.001$), and the high triglyceride ($F = 32.81$; $P < 0.001$) traits rendered this relationship virtually unchanged. In contrast, the positive association between the number of metabolic traits and CRP was no longer significant (Fig. 1B) after adjustment for the low HDL cholesterol criterion ($F = 0.87$; $P = 0.352$).

CONCLUSIONS— From our data, we conclude that among angiographed coronary patients CRP is strongly associated with the MetS but not with angiographically characterized coronary atherosclerosis. Specifically, the overall association of the MetS with CRP is driven by the low HDL cholesterol feature.

Data from the literature on the association of CRP with cross-sectionally determined CAD are controversial. Most studies have not found such an association (2,9–12). This observation likely reflects the fact that inflammation is not associated with plaque burden itself but rather with plaque vulnerability and rupture. Thus, our data do not contradict the numerous reports on an association between CRP and clinical atherothrombotic events.

Further, our data show that the low HDL cholesterol MetS feature drives the

overall association between the MetS and CRP; CRP was no longer associated with the number of MetS traits when adjusted for HDL cholesterol. These data fit into the notion that HDL particles, besides their crucial role in reverse cholesterol transport, also protect the artery wall through anti-inflammatory mechanisms (13). Thus, CRP is strongly associated with the MetS but not with angiographically diagnosed coronary atherosclerosis. The overall association of the MetS with CRP is predominantly driven by the low HDL cholesterol feature, a paramount predictor of vascular events.

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