Roles of the metabolic syndrome, HDL cholesterol, and coronary atherosclerosis in subclinical inflammation

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**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 1010 patients undergoing coronary angiography; coronary stenoses ≥50% were considered significant; the MetS was defined according to AHA revised NCEP-ATP-III criteria.

**Results:** 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-C \( (p<0.001) \), large waist \( (p<0.001) \), high glucose \( (p<0.001) \) and high blood pressure \( (p=0.016) \) but not the high triglycerides \( (p=0.352) \) proved associated with CRP. When all MetS traits were considered simultaneously, only low HDL-C 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-C feature.
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) 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 1047 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 ≥50% were considered significant (5,6). The MetS was diagnosed according to AHA revised NCEP ATP-III criteria (7). The Ethics Committee of the University of Innsbruck approved the study; all participants gave written informed consent.

**Analytical procedures and statistical analyses:** Analytical procedures were performed on a Cobas Integra 800® (Roche, Basle, Switzerland), as described previously (4,8). Sample size calculations showed that assuming a standard deviation 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 alpha-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 the MetS than in subjects without the MetS (59.5% vs. 52.8%; p=0.034); adjustment for age, gender, LDL-cholesterol, smoking, cardiovascular medications (statins, aspirin, ACE inhibitors/angiotensin-receptor blocking agents and beta-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 [1.11–2.22]; p=0.011) and the high glucose traits (OR=1.33 [1.02–1.73]; p=0.038) proved significantly and independently of the above covariates associated with significant CAD, whereas the high triglycerides (p=0.082), the large waist (p=0.826), and the high blood pressure criteria (p=0.145) were not independently associated with significant CAD.

**CRP, the MetS and CAD:** CRP was significantly higher in patients with the MetS than in subjects without the MetS (0.46±0.62 vs. 0.35±0.49 mg/dl; p=0.001). In contrast, CRP did not differ significantly 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 to 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, gender, LDL-cholesterol, smoking, cardiovascular medications and
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The presence of the MetS (standardized adjusted OR 0.97 [0.76–1.25]; p=0.822).

Considering both the MetS and significant CAD, CRP was significantly higher in patients with the 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 the MetS (p=0.869) nor among subjects with the MetS (p=0.411).

Analysis of covariance (ANCOVA) adjusting for age, gender, LDL-cholesterol, smoking, and cardiovascular medications confirmed that the 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 criteria (p<0.001) but not in patients who fulfilled the high triglyceride criterion (p=0.352) compared to patients who did not fulfill the respective MetS criteria. When all MetS traits were entered simultaneously into one ANCOVA model, only low HDL-cholesterol proved associated with CRP (F=44.19; p<0.001) independently of age, gender, LDL-cholesterol, smoking, major cardiovascular medications and of all other MetS criteria.

CRP increased significantly (p<0.001) with an increasing number of metabolic syndrome traits (Figure 1A) after adjustment for age, gender, 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 traits (F=32.81; p<0.001) 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 angiographied 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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article. Christoph H. Saely contributed to the concept and design of the study; to the collection of data; to analysis and interpretation of data; and to drafting the article. Stefan Beer contributed to the collection of data; to analysis and interpretation of data; and to revising the manuscript for important intellectual content. Alexander Vonbank contributed to the collection of data; to analysis and interpretation of data; and to revising the manuscript for important intellectual content. Heinz Drexel contributed to the concept and design of the study; to the collection of data; to analysis and interpretation of data; and to drafting the article. All authors approved the final version of the manuscript to be published. Philipp Rein and Christoph H. Saely contributed equally to this work.

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**Figure legends:**

**Figure 1.** Relationship of the number of metabolic syndrome components and CRP adjusted for age, gender, LDL cholesterol, smoking and major cardiovascular medications in (A); further adjustment for the low HDL criterion in (B); CRP denotes C-reactive protein; p value is given for the association of CRP with the number of metabolic syndrome components.
A

CRP (mg/dl)

0

0.2

0.4

0.6

0.8

1.0

Number of Metabolic Syndrome Components

B

CRP (mg/dl)

0

0.2

0.4

0.6

0.8

1.0

Number of Metabolic Syndrome Components

p < 0.001

p = 0.352