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

PHILIPP REIN, MD[1,2,3*]
CHRISTOPH H. SAELY, MD[1,2,3*]
STEFAN BEER, MD[1,2,3]
ALEXANDER VONBANK, MD[1,2,3]
HEINZ DREXEL, MD[1,2,3,4]

**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 ≥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.

*Diabetes Care* 33:1853–1855, 2010

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 ≥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 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, 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-

From the [1]Vorarlberg Institute for Vascular Investigation and Treatment, Feldkirch, Austria; the [2]Department of Medicine and Cardiology, Academic Teaching Hospital Feldkirch, Feldkirch, Austria; the [3]Private University of the Principality of Liechtenstein, Triesen, Liechtenstein; and the [4]Drexel University College of Medicine, Philadelphia, Pennsylvania.
Corresponding author: Heinz Drexel, vivit@lkhf.at.
Received 30 December 2009 and accepted 5 May 2010. Published ahead of print at http://care.diabetesjournals.org on 18 May 2010. DOI: 10.2337/dc09-2376.
*P.R. and C.H.S. contributed equally to this article.

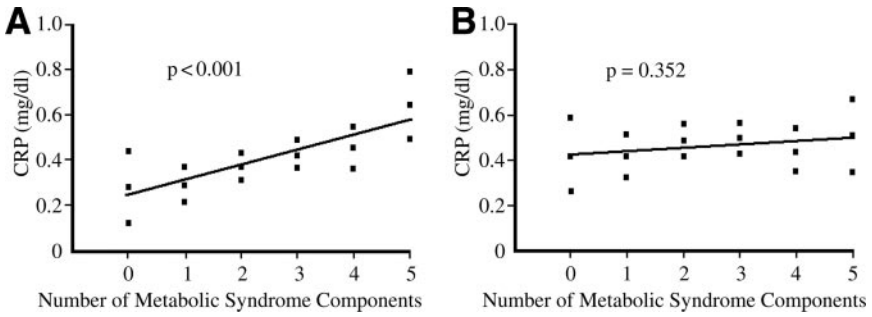


**Figure 1—**A*: Relationship of the number of MetS components and CRP adjusted for age, sex, LDL cholesterol, smoking, and major cardiovascular medications.* B*: Further adjustment for the low HDL criterion.* P *value is given for the association of CRP with the number of MetS components.*

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 simultaneously 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 ($P_{trend} < 0.001$) with an increasing number of MetS traits (Fig. 1*A*) 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. 1*B*) 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.

**Acknowledgments**— The Vorarlberg Institute for Vascular Investigation and Treatment thanks the government of Vorarlberg, Abteilung der Landesregierung IIb and VI; Dr. Karl Josef Hier; the Peter Goop Stiftung (Vaduz, Liechtenstein); the Fachhochschule Dornbirn (Dornbirn, Austria); and the Institute for Clinical Chemistry at the Academic Teaching Hospital Feldkirch (Feldkirch, Austria) for providing us with generous research grants. The study was financed in part by the Land Vorarlberg and the Europaeischer Fonds fuer regionale Entwicklung.

No potential conflicts of interest relevant to this article were reported.

P.R. 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. C.H.S. 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. S.B. contributed to the collection of data, to analysis and interpretation of data, and to revising the manuscript for important intellectual content. A.V. contributed to the collection of data, to analysis and interpretation of data, and to revising the manuscript for important intellectual content. H.D. 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.

We are grateful to Franz Rauch and the Vorarlberger Industriellenvereinigung (Bregenz, Austria); to Dr. Peter Woess and the Vorarlberger Aerztekammer (Dornbirn, Austria); to Mag. Gabriela Duer and the Vorarlberger Landesregierung; to Dr. Elmar Bechter, Landessanitätsdirektor (Bregenz, Austria); and to Luis Patsch, former Director, Vorarlberger Landeskrankenhaus-Betriebsgesellschaft, for continuously supporting our Research Institute.

### References

1. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease de-

tection and prevention. Circulation 2003; 107:363–369
2. Jenny NS, Brown ER, Detrano R, Folsom AR, Saad MF, Shea S, Szklo M, Herrington DM, Jacobs DR Jr. Associations of inflammatory markers with coronary artery calcification: results from the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis 2010;209:226–229
3. Zebrack JS, Muhlestein JB, Horne BD, Anderson JL. C-reactive protein and angiographic coronary artery disease: independent and additive predictors of risk in subjects with angina. J Am Coll Cardiol 2002;39:632–637
4. Saely CH, Koch L, Schmid F, Marte T, Aczel S, Langer P, Hoefle G, Drexel H. Adult Treatment Panel III 2001 but not International Diabetes Federation 2005 criteria of the metabolic syndrome predict clinical cardiovascular events in subjects who underwent coronary angiography. Diabetes Care 2006;29:901–907
5. Kip KE, Marroquin OC, Kelley DE, Johnson BD, Kelsey SF, Shaw LJ, Rogers WJ, Reis SE. Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE) study. Circulation 2004;109: 706–713
6. Drexel H, Amann FW, Beran J, Rentsch K, Candinas R, Muntwyler J, Luethy A, Gasser T, Follath F. Plasma triglycerides and three lipoprotein cholesterol fractions are independent predictors of the extent of coronary atherosclerosis. Circulation 1994;90:2230–2235
7. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112: 2735–2752
8. Saely CH, Vonbank A, Rein P, Woess M, Beer S, Aczel S, Jankovic V, Boehnel C, Risch L, Drexel H. Alanine aminotransferase and gamma-glutamyl transferase are associated with the metabolic syndrome but not with angiographically determined coronary atherosclerosis. Clin Chim Acta 2008;397:82–86
9. Arroyo-Espliguero R, Avanzas P, Cosin-Sales J, Aldama G, Pizzi C, Kaski JC. C-reactive protein elevation and disease activity in patients with coronary artery disease. Eur Heart J 2004;25:401–408
10. Azar RR, Aoun G, Fram DB, Waters DD, Wu AH, Kiernan FJ. Relation of C-reactive protein to extent and severity of coronary narrowing in patients with stable angina pectoris or abnormal exercise tests. Am J Cardiol 2000;86:205–207
11. Erren M, Reinecke H, Junker R, Fobker M, Schulte H, Schurek JO, Kropf J, Kerber S, Breithardt G, Assmann G, Cullen P. Systemic inflammatory parameters in patients with atherosclerosis of the coronary and peripheral arteries. Arterioscler Thromb Vasc Biol 1999;19:2355–2363
12. Grammer TB, Marz W, Renner W, Bohm BO, Hoffmann MM. C-reactive protein genotypes associated with circulating C-reactive protein but not with angiographic coronary artery disease: the LURIC study. Eur Heart J 2009;30:170–182
13. Rohrer L, Hersberger M, von Eckardstein A. High density lipoproteins in the intersection of diabetes mellitus, inflammation and cardiovascular disease. Curr Opin Lipidol 2004;15:269–278