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# Insulin resistance is associated with the metabolic syndrome and is not directly linked to coronary artery disease

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ABSTRACT

*Background:* Insulin resistance (IR) is the key feature of the metabolic syndrome (MetS). Its association with directly visualized coronary atherosclerosis is unclear. We hypothesised that insulin resistance is associated with both angiographically determined coronary artery disease (CAD) and with the MetS.
*Methods:* In 986 consecutive patients undergoing coronary angiography for the evaluation CAD, IR was determined by the HOMA index; the MetS was defined according to NCEP-ATPIII criteria; and significant CAD was diagnosed when coronary stenoses ≥50% were present.
*Results:* HOMA IR scores were higher in MetS patients than in subjects without the MetS (4.9 ± 6.4 vs. 2.2 ± 2.0; $p<0.001$). HOMA IR did not differ significantly between patients with significant CAD and those who did not have significant CAD. When both, the presence of MetS and of significant CAD were considered, HOMA IR was significantly higher in patients with the MetS both among those who had significant CAD (4.9 ± 6.8 vs. 2.2 ± 1.8; $p<0.001$) and among those who did not have significant CAD (5.0 ± 5.8 vs. 2.1 ± 2.3; $p<0.001$), it did not differ significantly between patients with significant CAD and subjects without significant CAD among patients with the MetS nor among those without MetS. Similar results were obtained with the IDF definition of the MetS.
*Conclusion:* IR is significantly associated with the MetS but not with angiographically determined CAD. IR may play a greater role in the eventual precipitation of thrombosis than in the gradual progression of atherosclerosis.



## 1. Introduction

Overweight and obesity have risen dramatically in the past several decades. This resulted in a marked increase in the prevalence of the metabolic syndrome (MetS), a cluster of cardiovascular risk factors including central adiposity, hypertension, dyslipidemia and impaired glucose metabolism [1–3]. According to Adult Treatment Panel III criteria (ATP III) [4] the MetS is diagnosed in the presence of at least 3 out of the 5 criteria: abdominal obesity, high triglycerides, low HDL cholesterol, elevated fasting glucose and high blood pressure. The such diagnosed MetS, as a clinical entity, substantially increases the risk of cardiovascular events both in the primary [5–8] and in the secondary [9] prevention settings [7,10–14]. In particular, the MetS confers an increased risk of premature coronary artery disease.

Pathophysiologically, insulin resistance is considered the key feature of the MetS [15]. Indeed, insulin resistance is associated with all component features of the MetS [16–18]. In epidemiological studies insulin resistance typically is quantified by the HOMA index. Importantly, insulin resistance significantly predicts cardiovascular events in prospective studies [19,20]. In particular, we could previously show that HOMA insulin resistance and the MetS are mutually independent predictors of future cardiovascular events [15]. Thus, HOMA insulin resistance contains prognostic information over and above the clinical entity of the MetS [15].

Of note, however, the association of insulin resistance with directly visualized atherosclerosis is unclear. This is a clinically important issue, because visualization of atherosclerosis represents other features of atherothrombotic disease than the clinical cardiovascular event does. The clinical cardiovascular event is precipitated by the rupture of an atherosclerotic plaque and subsequent thrombotic vessel obliteration. Thus, both atherosclerotic and thrombotic processes are involved. Importantly, however, risk factors driving the progress of atherosclerosis are not identical to the risk factors

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enhancing thrombosis. For example, myocardial infarction, a frequently applied endpoint in clinical studies, does not optimally reflect the atherogenicity of metabolic parameters. It is the last step in the development of atherothrombotic coronary artery disease (CAD), and thrombogenic factors ultimately determine whether or not infarction occurs [21,22]. By coronary angiography, to the opposite, preferentially atherosclerosis is assessed. Therefore, in order to assess the atherogenicity of risk factors it appears important to also investigate their association with angiographically determined coronary atherosclerosis.

We therefore determined HOMA insulin resistance in a large cohort of angiographically characterized coronary patients. We hypothesised that insulin resistance is associated with both angiographically determined CAD and with the MetS.

## 2. Materials and methods

### 2.1. Study subjects

From August 2005 through December 2007 we enrolled 986 consecutive Caucasian patients who were referred to elective coronary angiography for the evaluation of established or suspected stable CAD. Patients undergoing coronary angiography for other reasons were not enrolled. In particular, no patients with acute coronary syndromes were enrolled, which appears important because acute coronary syndromes have the potential to transiently alter metabolic characteristics including lipid parameters and fasting glucose [23]. Six patients with type 1 diabetes and 49 patients with insulin therapy were excluded from the analyses. From our patients, 134 had previously undergone angioplasty and 51 had previously received coronary artery bypass grafts.

Information on conventional cardiovascular risk factors was obtained by a standardized interview; and systolic/diastolic blood pressure was measured by the Riva–Rocci method under resting conditions in a sitting position at the day of hospital entry at least 5 h after hospitalization. Hypertension was defined according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [24], and type 2 diabetes mellitus (T2DM) was diagnosed according to World Health Organization criteria [25].

Height and weight were recorded, and body mass index (BMI) was calculated as body weight (kg)/height $(m)^2$. Overall, 69.5% of our patients were on aspirin, 49.7% on statins, 1.4% on fibrates, 11.9% on calcium antagonists, 55.2% on beta adrenoreceptor blocking agents, 24.9% on diuretics, 35.4% on angiotensin converting enzyme inhibitors, and 18.7% on angiotensin II receptor blocking agents. Among patients with T2DM, 33.7%, 53.7%, 0.6%, and 3.4% were receiving – alone or in combination – sulfonylurea, metformin, acarbose, and glitazones, respectively.

According to National Cholesterol Education Programme ATP-III criteria (NCEP-ATPIII) [26], the MetS was diagnosed in the presence of any three of: waist circumference >102 cm in men and >88 cm in women, triglycerides ≥150 mg/dl (1.7 mmol/l), high density lipoprotein (HDL) cholesterol <40 mg/dl (1.0 mmol/l) in men and <50 mg/dl (1.3 mmol/l) in women, blood pressure ≥130/≥85 mm Hg, or fasting glucose ≥100 mg/dl (5.6 mmol/l). Using International Diabetes Federation (IDF) criteria [27] , the MetS was diagnosed in patients who had a large waist circumference (≥94 cm in men and ≥80 cm in women) plus any two of: triglycerides ≥150 mg/dl (1.7 mmol/l) or specific treatment for this lipid abnormality, high density lipoprotein (HDL) cholesterol <40 mg/d (1.0 mmol/l) in males and <50 mg/dl (1.3 mmol/l) in females or specific treatment for this lipid abnormality, systolic blood pressure ≥130 or diastolic blood pressure ≥85 mm Hg or treatment of previously diagnosed hypertension, and fasting plasma glucose ≥100 mg/dl (5.6 mmol/l) or previously diagnosed T2DM.

Coronary angiography was performed with the Judkin's technique. Stenosis severity was assessed by visual inspection by a team of two investigators who were blinded to serologic assays. Coronary artery stenoses with lumen narrowing ≥50% were considered significant, the extent of CAD was defined as the number of significant coronary stenoses in a given patient, and coronary arteries were defined as normal in the absence of any visible lumen narrowing at angiography, as described previously [28]. The Ethics Committee of the University of Innsbruck approved the present study, and all participants gave written informed consent.

### 2.2. Laboratory analyses

Venous blood samples were collected after an overnight fast of 12 h before angiography was performed, and laboratory measurements were performed from fresh serum samples, as described previously [29]. Serum triglycerides, total cholesterol, low density lipoprotein (LDL) cholesterol, HDL cholesterol, apolipoprotein B, apolipoprotein A1, CRP, and plasma glucose were determined on a Cobas Integra 800® (Roche, Basel, Switzerland).

Hemoglobin A1c (HbA1c) was determined by high-performance liquid chromatography on an ADAMS A1c HA-8160® (Menarini, Florenz, Italy). Plasma insulin was measured with a Roche Cobas E601® (Roche, Basel, Switzerland). HOMA index was calculated by the formula fasting insulin [μU/ml] × fasting glucose [mg/dl]/405 [30].

### 2.3. Statistical analysis

Differences in patient characteristics were tested for statistical significance with the Chi square test for categorical variables; the Mann–Whitney-U and Kruskal–Wallis tests were used for continuous variables, as appropriate. Spearmen rank correlation coefficients were calculated. To test for independent determinants of continuous variables, analysis of covariance (ANCOVA) was performed, using a general linear model approach. Results are given as mean ± standard deviation if not denoted otherwise. P-values <0.05 were considered significant. 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 HOMA insulin resistance scores of 20% with a power of 80% at an alpha-fault of 0.05. Statistical analyses were performed with the software package SPSS 11.0 for Windows (SPSS, Inc., Chicago, IL).

## 3. Results

### 3.1. Patient characteristics

Overall, the characteristics of our study population were typical for a cohort undergoing coronary angiography for the evaluation of CAD, with a preponderance of male gender (64.6%), and a high prevalence of T2DM (19.4%), hypertension (80.8%), and smoking (59.2%). Overall, 330 (35.5%) of our patients had the MetS as defined by NCEP-ATP-III criteria, and in 510 patients (54.9%) coronary angiography revealed significant CAD with coronary stenoses ≥50%.

From our patients, 280 had neither the MetS (ATP-III definition) nor significant CAD, 144 had the MetS, but not significant CAD, 304 did not have the MetS but had significant CAD, and 203 had both, the MetS and significant CAD. Table 1 summarizes characteristics of our patients in these four groups.

### 3.2. Insulin resistance in study groups

HOMA insulin resistance scores were significantly higher in MetS patients than in subjects without the MetS (4.9 ± 6.4 vs. 2.2 ± 2.0; p<0.001). In contrast, HOMA insulin resistance did not differ significantly between patients with significant CAD and those who