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The metabolic syndrome predicts incident congestive heart failure: A 20-year follow-up study of elderly finns

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ABSTRACT

Objective: We investigated whether the metabolic syndrome (MetS) and its components defined by four different criteria including subjects with prevalent diabetes in their definitions were associated with congestive heart failure (CHF) independent of interim myocardial infarction (MI) and prevalent diabetes during a 20-year follow-up in an elderly population-based study.
Methods and results: The MetS was defined according to the World Health Organization (WHO), the National Cholesterol Education Program (NCEP), the International Diabetes Federation (IDF), and the American Heart Association and the National Heart, Lung, and Blood Institute (AHA) criteria. The association of the MetS with incident CHF (303 cases) was investigated with Cox regression analyses in a 20-year follow-up study of 1032 Finns, aged 65–74 years at baseline. Among all subjects the MetS by all four criteria was significantly associated with a 1.45–1.74-fold risk for incident CHF after the adjustment for confounding factors. When subjects with interim MI during the follow-up and with prevalent diabetes were excluded, the MetS was significantly associated with a 1.37–1.87-fold risk for incident CHF after the adjustment for confounding factors. Of the single components of the MetS, the following were associated with incident CHF: impaired fasting glucose (IFG) [fasting plasma glucose (FPG) $\geq$ 6.1 mmol/l, Hazards ratio (HR) 1.46 or FPG $\geq$ 5.6 mmol/l, HR 1.62)]; raised blood pressure (BP) [(BP $\geq$ 140/90 mmHg or antihypertensive medications, HR 1.89); central obesity (waist circumference $\geq$ 94 cm in men or $\geq$80 cm in women, HR 1.49); (waist circumference $\geq$102 cm in men or $\geq$88 cm in women, HR 1.48); obesity (body mass index $\geq$ 30 kg/m^2, HR 1.79); and low high-density lipoprotein cholesterol (<1.03 mmol/l in men or <1.29 mmol/l in women, HR 1.55).
Conclusions: The MetS defined by four different criteria predicted CHF independent of interim MI and prevalent diabetes in elderly Finns, but not above and beyond the risk associated with one component of the MetS, hypertension.

1. Introduction

Congestive heart failure (CHF) is responsible for a large and still growing proportion of cardiovascular morbidity and mortality. Hypertension and coronary heart disease (CHD) are considered to be the main causes of CHF. Other established risk factors for CHF are left ventricular hypertrophy (LVH), valvular heart disease, diabetes, cigarette smoking, obesity and dyslipidemia [1–4]. The metabolic syndrome (MetS), a clustering of cardiovascular risk factors conferring an increased risk of cardiovascular disease (CVD), has been defined by a variety of organizations, including the World Health Organization (WHO) in 1999 [5], the European Group for the Study of Insulin Resistance (EGIR) in 1999 [6], the National Cholesterol Education Program (NCEP) Expert Panel in 2001 [7], American College of Endocrinology (ACE) in 2003 [8], the International Diabetes Federation (IDF) in 2005 [9], and the American Heart Association and the National Heart, Lung, and Blood Institute (AHA criteria) in 2005 [10]. Since these different definitions were published, a few prospective studies have reported that the MetS defined by the NCEP criteria predicts CHF [11–15]. However, none of them investigated the effect of the

Abbreviations: ACE, American College of Endocrinology; ACR, the ratio of urinary albumin to urinary creatinine; AHA, American Heart Association; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; CHF, congestive heart failure; EGIR, European Group for the Study of Insulin Resistance; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HR, hazard ratio; IDF, International Diabetes Federation; MetS, metabolic syndrome; MI, myocardial infarction; NCEP, National Cholesterol Education Program; OGTT, oral glucose tolerance test; 2-h PG, 2-h post glucose load; WHO, World Health Organization; WHR, waist-to-hip ratio.

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MetS defined by the other definitions on incident CHF. Therefore, it is not known if different definitions of the MetS equally predict CHF. In particular, it is unknown whether the MetS predicts CHF independent of myocardial infarction (MI) and diabetes. It is also unknown whether the MetS predicts CHF beyond and above its single components. Therefore, the aim of the present study was to investigate the association of the MetS and its single components, defined by the four criteria of the MetS, which include patients with prevalent diabetes (WHO, NCEP, IDF and AHA criteria), with the risk of CHF in an elderly cohort of Finnish subjects with and without interim MI and prevalent diabetes during a 20-year follow-up.

2. Materials and methods

2.1. Baseline study

The formation [16] and representativeness [17] of the study population have been described in detail previously. Briefly, the study was conducted in Kuopio, east Finland, between 1986 and 1988. Altogether 1910 subjects born between 1912 and 1921 were randomly selected from the population register including all inhabitants of Kuopio. This random sample covered 35% of all residents in the age group of 65–74 years. The overall participation rate was 71%. All subjects with CHF at baseline ($n = 267$) were excluded. A total of 1032 study subjects aged 65–74 years at baseline were included in the present study.

Weight, height, waist and hip circumference, and blood pressure (BP) were measured at baseline. Blood pressure was measured in the supine position with a mercury sphygmomanometer after a 5-min rest. Two readings were taken (interval 1.5 min) and the latter one was used in statistical analyses. Waist-to-hip ratio (WHR) was defined as waist circumference to hip circumference. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Smoking status was defined as current smoking. Antihypertensive medications were dichotomized. With respect to alcohol consumption, subjects were classified as alcohol users or nonusers. Physical activity during leisure time was classified as physically inactive (little and occasional activity) and physically active (regular exercise at least once a week and at least 30 min per time).

Blood samples were taken in the morning after a 12-h overnight fast. All subjects, except for those receiving insulin, underwent an oral glucose tolerance test (OGTT) (75 g glucose). Plasma glucose and insulin, serum lipids and lipoproteins, and urinary albumin were determined as previously described [16,18]. Ratio of urinary albumin (mg/l) to urinary creatinine (mmol/l) (ACR) was used as a measure of albumin excretion.

At baseline, the WHO criteria [5] was used to diagnose type 2 diabetes in subjects without previously known diabetes based on fasting plasma glucose (FPG) and 2-h post glucose load (2-h PG) values in an oral glucose tolerance test (OGTT). The diagnosis of previously known diabetes was based on antidiabetic medications or a history of a diagnosis of diabetes made by a physician. Of 1032 study subjects, 77 had known diabetes and 98 had newly diagnosed diabetes at the baseline study.

Electrocardiographic LVH at baseline was defined according to the Minnesota code (codes 3.1 or 3.3) [19].

Previous verified definite and possible myocardial infarction (MI) prior the baseline study was defined according to the WHO MONICA project criteria [20] as modified by the FINMONICA AMI Register Study Group [21]. Subjects with interim MI were defined as those without MI at baseline who developed MI during the follow-up.

The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of Kuopio University Hospital. All study subjects gave informed consent.

2.2. Definitions of the MetS

The present study was based on the WHO, NCEP, IDF and AHA definitions, which include subjects with diabetes in their definitions. EGIR and ACE criteria, which exclude diabetic subjects in their definitions, were not used. Each component of the four definitions was defined according to the original criteria. Criteria for the four definitions of the MetS are shown in Table 1.

2.3. Definition of CHF

2.3.1. Baseline

In Finland, drug treatment of all subjects with verified CHF are reimbursed by the Social Insurance Institution. The diagnosis of CHF is made by a specialist, and it is based on diagnostic and etiological examinations. A certificate written by a specialist must include information on the etiology of CHF, and on the need of medication more than six months. Study subjects with CHF at baseline ($n = 267$) were identified from the Social Insurance Institution Reimbursement Registry of Finland. Of them 33 subjects also had medical records of the Kuopio University Hospital, including detailed information on the diagnosis, etiology, drug treatment and echocardiography. All subjects had diseases increasing the susceptibility to CHF (64% of them had hypertension, 53% MI, 30% CHD, 42% chronic *atrial fibrillation*, and 27% type 2 diabetes). All subjects were at least on one of the following medications: beta-blockers, ACE inhibitors, angiotensin receptor antagonists, diuretics, and digitalis (36% of them were receiving at least three of the medications).

2.3.2. Follow-up

Subjects with incident CHF ($n = 303$) prior to the end of June 2008 were identified from the medical records of the Kuopio University Hospital. Detailed information on the diagnosis, etiology, drug treatment and echocardiography were obtained. All subjects had diseases increasing the risk of CHF [62% had hypertension (BP $\geq$ 140/90 mmHg or the use of antihypertensive medication), 44% MI, 34% CHD, 46% chronic *atrial fibrillation*, 28% type 2 diabetes, and 1% dilated cardiomyopathy]. All subjects were at least on one of the following medications: beta-blockers, ACE inhibitors, angiotensin receptor antagonists, diuretics, or digitalis (41% of them were at least on three medications). Echocardiography had been performed among 85 subjects with incident CHF at the time of diagnosis, and 41% of them had ejection fraction < 50%.

2.4. Statistical analyses

All statistics were performed with the SPSS 14.0 statistical programs. Because of the skewed distribution of fasting insulin, triglycerides and ACR concentrations, these variables were log transformed for statistical analyses. Differences in baseline characteristics between subjects with and without incident CHF were tested by Chi square test and Student's t test. The multivariable Cox regression analyses were applied to investigate the association of the MetS defined by the four criteria with incident CHF. Each definition was used as a predictor and the covariates included age, gender, physical activity during leisure time, smoking, alcohol consumption, antihypertensive medications, total cholesterol, and prevalent diabetes (Model 1 in Table 3). To evaluate whether the MetS predicted CHF independent of an interim MI during the follow-up and prevalent diabetes, we performed Cox analysis when subjects with interim MI during the follow-up were excluded from