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Metabolic syndrome and the risk of sudden cardiac death in middle-aged men☆

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ABSTRACT

Background: Little is known about the relationship between metabolic syndrome and sudden cardiac death (SCD). We examined the association of metabolic syndrome, as defined by World Health Organization (WHO), International Diabetes Federation (IDF), National Cholesterol Education Program (NCEP) and American Heart Association (AHA) — IDF interim criteria, with incident SCD. We also assessed the association of a continuous metabolic risk score with SCD.
Methods: A total of 1466 middle-aged men participating in a prospective population-based cohort study from eastern Finland with no history of coronary heart disease or diabetes at baseline were included.
Results: During the average follow-up of 21 years 85 SCDs occurred. Men with the metabolic syndrome as defined by the WHO, NCEP, IDF and interim criteria had a 2.2–2.6 fold, increased risk for SCD, after adjusting for lifestyle and traditional cardiovascular risk factors not included in the metabolic syndrome definition ($P < 0.001$–0.011). A one-standard deviation increase in the metabolic risk score (composed of the sum of Z-scores for waist circumference, insulin, glucose, high-density lipoprotein (HDL) cholesterol, triglycerides, and blood pressure) was associated with a 1.68-fold higher (95% CI 1.33-2.11) risk of SCD. Even when adjusting further for systolic blood pressure, HDL cholesterol and body mass index, the association remained significant for the interim criteria and the metabolic risk score, but not for WHO, NCEP, or IDF definitions.
Conclusions: Men with metabolic syndrome are at increased risk for SCD. Incident SCD associated with the IDF/AHA interim criteria and metabolic risk clustering estimated by a score is not explained by obesity or traditional cardiovascular risk factors.
Key messages: Men with metabolic syndrome are at increased risk for sudden cardiac death. Incident sudden cardiac death associated with metabolic risk clustering estimated by a score in not explained by obesity or traditional cardiovascular risk factors. Prevention of the metabolic syndrome may help reduce the health burden of SCD.

1. Introduction

Sudden cardiac death (SCD) accounts for one-half of all coronary heart disease (CHD)-related deaths. Since a majority of SCDs occur among the general segments of the population, the problem would require screening methods applicable to the general population. There continues to be interest in identifying clinically useful markers for SCD among the general population. Epidemiological studies have shown that half of the victims of SCD have no physician-diagnosed CHD at the time of death [1–2].

Metabolic syndrome (MetS) is a common clinical condition with a prevalence varying from 10 to 40%, or even higher in older age groups, depending on the populations and definition of MetS [3–12]. A previous study found increased SCD risk for the metabolic syndrome based on the definitions of National Cholesterol Education Program III (NCEP-ATPIII) and International Diabetes Federation (IDF) with respect to SCD [3]. However, this previous study did not evaluate the risk of MetS for SCD based on World Health Organization (WHO) definition. Current definitions may also be criticized for the use of arbitrary dichotomous cut-offs for the features of the metabolic syndrome, even though

☆ All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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risk factors such as blood pressure and high-density lipoprotein (HDL) cholesterol have continuous and dose-related associations with cardiovascular outcomes. Some researchers have therefore estimated metabolic risk as a continuous variable using the sum of the Z-scores of the individual metabolic risk factors [13,14].

The objective of the present investigation was to evaluate SCD risk for the MetS as defined by the WHO, NCEP, IDF and IDF/American Heart Association (AHA) interim criteria and a metabolic risk score in a population-based cohort of middle-aged men who did not have coronary heart disease or diabetes at baseline.

2. Research design and methods

2.1. Subjects

This study group was subgroup of a random sample of 3433 men aged 42 to 60 years who resided in the town of Kuopio or its surrounding rural communities in eastern Finland. Of those invited, 2682 (83%) participated in the study. This Kuopio Ischemic Heart Disease Study (KIHD) was designed to investigate risk predictors for atherosclerotic cardiovascular outcomes in a population-based sample of men [7]. For the present study men with diabetes (n = 174) or CHD (n = 677) at baseline were excluded. Men with missing data (n = 615) on waist circumference or biochemical values included in the definition of the metabolic syndrome were excluded leaving 1466 for the analyses.

2.2. Assessment of components of the metabolic syndrome

Blood pressure was measured with a random-zero sphygmomanometer. The mean of 6 measurements (3 while supine, 1 while standing, and 2 while sitting) of systolic and diastolic blood pressure was used. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was calculated as the average of 2 measurements taken after inspiration and expiration at the midpoint between the lowest rib and iliac crest. Waist-hip ratio was defined as waist girth/hip circumference measured at the trochanter major.

Participants were asked to fast and to refrain from smoking for 12 h and to avoid alcohol intake for 3 days before blood sampling. Blood glucose was measured using a glucose dehydrogenase method after precipitation of proteins by tricholoracetic acid. Insulin was measured with a radioimmunoassay kit (Novo Nordisk, Bagsvaerd, Denmark) from the serum samples stored at −80 °C [7]. Because blood glucose was measured instead of plasma glucose, a blood glucose value of 5.6 mmol/L was considered to correspond to a plasma glucose level of 6.1 mmol/L [4], and a blood glucose value of 5.0 mol/L to correspond to a plasma glucose value of 5.6 mmol/L. Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) fractions were separated from fresh serum by combined ultracentrifugation and precipitation. Lipoprotein fraction cholesterol and triglycerides were measured enzymatically [15].

2.3. Metabolic syndrome

As suggested by the European Group for the Study of Insulin Resistance, hypertension was defined at a lower level (at least 140/90 mm Hg or blood pressure medication) than the original WHO definition for consistency with the WHO-International Society of Hypertension and Sixth Joint National Committee recommendations [7,16–17], and microalbuminuria was not included in the definition [16]. The original WHO cut-off for serum HDL cholesterol was maintained. Abdominal obesity was defined according to the original WHO definition (waist-hip ratio >0.90 or BMI ≥30).

The International Diabetes Federation consensus proposed a definition of MetS [18]. The MetS was defined as the presence of abdominal adiposity and two or more abnormalities of the following: elevated triglycerides (≥150 mg/dL or 1.7 mmol/L) or specific treatment for dyslipidemia, low HDL cholesterol (<40 mg/dL or 1.0 mmol/L for men), elevated fasting plasma glucose (≥100 mg/dL or 5.6 mmol/l) or antidiabetic treatment and elevated systolic or diastolic blood pressure (≥130/85 mm Hg) or antihypertensive medications.

The MetS defined by the NCEP-ATPIII was the presence of 3 or more of the following: fasting plasma glucose of at least 110 mg/dL (6.1 mmol/L), serum triglycerides of at least 150.0 mg/dL (1.7 mmol/L), serum HDL cholesterol less than 40 mg/dL (1.04 mmol/L), blood pressure of at least 130/85 mm Hg, or waist girth of more than 102 cm. Use of waist girth of more than 94 cm was suggested for men genetically susceptible to insulin resistance [19]. In keeping with the clinically oriented NECP-ATPIII recommendations, the cut off for HDL cholesterol was rounded off in SI units (<1.0 mmol/L) [20].

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The IDF and AHA and several other organizations proposed an interim definition based on the presence of 3 or more of the following: fasting plasma glucose of at least 100 mg/dL (5.6 mmol/L), serum triglycerides of at least 150 mg/dL (1.7 mmol/L), serum HDL cholesterol less than 40 mg/dL (1.0 mmol/L), blood pressure of at least 130/85 mm Hg or blood pressure medication, or abdominal obesity using population-specific waist circumference [20]. A cut-off for waist of either 94 cm or 102 cm was suggested for europoid populations. For our study we used a cut-off of 94 cm.

2.4. Calculation of the metabolic risk score

We calculated a continuous metabolic risk score (Metscore) similarly to previously published scores [21] using the sum of continuous Z-scores; waist circumference + insulin + glucose − HDL cholesterol + triglycerides + the average of SBP and DBP. A higher MetS score indicates a less favorable metabolic risk profile.

2.5. Assessment of risk factors

Assessment of smoking, alcohol consumption, diet, socioeconomic status, medical history and medications and family history of diseases have been described previously [7,15,22].

2.6. Classification of sudden cardiac death

All deaths that occurred by the end of 2009 were checked from the hospital documents, wards of health centers and death certificates. Deaths were coded using to the Ninth International Classification of Diseases codes or the Tenth International Classification of Diseases codes. The sources of information were interviews, hospital documents, death certificates, autopsy reports and medico-legal reports [22]. There were no losses to follow-up.

A death was determined SCD when it occurred either within 1 h after the onset of an abrupt change in symptoms or within 24 h after onset of an abrupt change in symptoms when autopsy data did not reveal a non-cardiac cause of sudden death. Sudden cardiac deaths that occurred out-of-hospital conditions were also defined based on hospital documents. Subjects who were successfully resuscitated from ventricular tachycardia (VT) or ventricular fibrillation (VF) were included in the definition of sudden cardiac arrest outcome. The deaths due to aortic aneurysm rupture, cardiac rupture or tamponade and pulmonary embolism, cancer or other non-cardiac co-morbidities were not included as SCD. The diagnostic classification of events was based on symptoms, electrocardiographic findings, cardiac enzyme elevations, autopsy findings (80%) and history of CHD together with the clinical and ECG findings of the paramedic staff. Thus, we have available all hospital documents including medical records, laboratory and ECG findings from hospital and paramedical staff and the use of medications and defibrillator. SCD cases were checked from deaths from cardiovascular causes and all available documents [22]. The documents related to the death were cross-checked in detail by two physicians. The independent event committee were blinded to clinical data performed classification of deaths.

2.7. Statistical analysis

Skewed variable was normalized by taking the log, or in the case of conditioning leisure-time physical activity, by taking the square root. Comparisons of baseline variables between men who died suddenly during the follow-up and those who did not were made using the unpaired Student's t-test or chi-square test. Relative risks of WHO, NCEP and IDF definitions of the MetS with SCD were estimated using forced Cox proportional hazard regression models with adjustment for age and examination year (model 1); age, examination year, socio-economic status, smoking, alcohol consumption, and family history of CHD, dietary intake of saturated fats, and energy expenditure on leisure time physical activity (model 2). Relative hazards, adjusted for risk factors, were estimated as antilogarithms of coefficients from multivariate models. All tests for statistical significance were two-sided. The fit of the proportional-hazard models was examined by plotting the hazard functions in different categories of risk factors over time. The proportional hazard assumptions met indicated that the application of the models was appropriate. All statistical analyses were performed using the SPSS 20.0 Windows software.

3. Results

3.1. Baseline characteristics and follow-up events

At the beginning of the follow-up, 15% out of 1381 men who did not suffer a SCD during the follow-up had the metabolic syndrome according to WHO definition, 8% had it according to the NCEP and IDF definitions, and 19% according to the IDF/AHA interim definition (Table 1). In men who died suddenly during the follow up (n = 85), the prevalence of the metabolic syndrome based on these definitions was about two-fold higher (p < 0.001–0.027). The metabolic risk score was also higher in men who died suddenly during the follow up (P = 0.001). When defining the metabolic syndrome at the top 20% of the metabolic risk score when classifying men with a MetSscore in the top 20% of the entire non-diabetic KIHD cohort (corresponding 18% in men without CHD or diabetes at baseline included in this study) as having the metabolic syndrome in our study population (corresponding to the