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Prospective study of metabolic syndrome as a mortality marker in chronic coronary heart disease patients

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ABSTRACT

Background: We aimed to clarify the impact of metabolic syndrome (MetS) as assessed by different definitions on the cardiovascular mortality in patients with coronary heart disease (CHD).
Methods: A total of 1692 patients, 6–24 months after myocardial infarction and/or coronary revascularization at baseline, were followed in a prospective cohort study. MetS was identified using four different definitions: standard National Cholesterol Education Program definition (NCEP-ATPIII) based on the presence of ≥3 of the following factors: increased waist circumference, raised blood pressure, hypetriglyceridemia, low high-density lipoprotein cholesterol, and increased fasting glycemia; modified NCEP-ATPIII definition (similar, but omitting antihypertensive treatment as an alternative criterion); presence of "atherogenic dyslipidemia"; or "hypertriglyceridemic waist". The primary outcome was a fatal cardiovascular event at 5 years.
Results: During 5-year follow-up, 117 patients (6.9%) died from a cardiovascular cause. Patients with MetS by modified NCEP-ATPIII ($n = 1066$, 63.0% of the whole sample) had significantly higher 5-year cardiovascular mortality [adjusted hazard risk ratio (HRR) 2.01 [95%CI:1.26–3.22]; $p = 0.003$] than subjects without MetS. However, when testing single MetS component factors, the majority of attributable mortality risk was driven by increased fasting glycemia (≥5.6 mmol/L) [HRR 2.69 (95%CI:1.29–5.62), $p = 0.009$] and the significance of MetS disappeared. None of the other MetS definitions, i.e., standard NCEP-ATPIII ($n = 1210$; 71.5%), "hypertriglyceridemic waist" ($n = 455$; 26.9%) or "atherogenic dyslipidemia" ($n = 223$; 13.2%) were associated with any significant mortality risk.
Conclusions: The co-incidence of MetS has a limited mortality impact in CHD patients, while an increase in fasting glycemia seems to be more a specific marker of mortality risk.

1. Introduction

In primary prevention, metabolic syndrome (MetS) is a widely accepted concept for identifying subjects who have at increased risk of developing diabetes mellitus and subsequent cardiovascular complications [1]. Typical phenotypes of the MetS include abdominal obesity (increased waist circumference), raised blood pressure, and dyslipidemia characterized by the following three parameters: high fasting triglycerides (TG), low high-density lipoprotein (HDL) cholesterol, and an increased relative amount of highly atherogenic, small low-density lipoprotein (LDL) particles [2,3]. It has been postulated that co-incidence of these phenotypes leads to an additive cardiovascular risk on top of the risk attributable to any of these factors acting singly. As a pathologic-anatomical correlate of MetS does not exist, all definitions of MetS are based only on consensus. They usually combine impaired glucose metabolism and the above typical phenotypes. The most accepted, so called "harmonized", definition comes from the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII) [3]. According to this definition, subjects with at least three out of five individual factors (increased waist circumference [according to population/country-specific definition]; raised blood pressure (BP) [systolic BP ≥ 130 and/or diastolic BP ≥ 85 mm Hg and/or antihypertensive treatment]); hypertriglyceridemia [≥1.7 mmol/L]; low HDL cholesterol [<1.0 or <1.3 mmol/L in males or females, respectively]; and increased fasting glucose [≥5.6 mmol/L and/or antidiabetic treatment] would qualify for MetS.

However, the application of this definition in subjects with manifest coronary heart disease (CHD) brings serious controversies. First, MetS is

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a concept built for identification of asymptomatic high-risk individuals in primary prevention, namely in generally healthy subjects without diabetes. It is questionable whether it can be transferred without modifications into secondary prevention, i.e. applied in chronically-ill patients, notably those with a very high prevalence of overt diabetes estimated to be somewhere between 27 and 55% in CHD patients across Europe [4]. Second, the usual NCEP-ATPIII definition is also seriously biased by the effects of drugs used by CHD patients routinely, typically beta-blockers or renin-angiotensin system (RAAS) blockers (this applies also to formally normotensive subjects). An alternative simplified approach to identify subjects with MetS adopted the following phenotypes as their criteria: "hypertriglyceridemic waist" [5] (triglycerides ≥2.0 mmol/L *plus* waist circumference ≥ 90/85 cm in males/females, respectively) or "atherogenic dyslipidemia" [6] (TG ≥ 1.7 mmol/L *plus* HDL < 1.0/1.2 mmol/L in males/females, respectively). However, use of these simplified definitions might be also improper in CHD patients. For example, dyslipidemia typical for MetS can be altered by treatment with statins, which have a moderate HDL-raising effect [7].

Therefore, the aim of the present study in stable patients with manifest CHD was to investigate the mortality impact of MetS assessed by the harmonized NCEP-ATPIII definition or by simplified concepts using only the most typical phenotypes. Moreover, we compared the predictive power of MetS using its components as individual risk factors.

2. Material and Methods

All procedures performed in this study were in accordance with the Good Clinical Practice principles and ethical standards formulated in the 1964 Declaration of Helsinki and its later amendments. The study protocols were approved by the Ethics Committees of the University Hospital in Pilsen and Institute for Clinical and Experimental Medicine in Prague. The data were stored and evaluated under the provisions of the Czech Data Protection Act. Written informed consent was obtained from all participants included in the study at baseline visit.

2.1. Design and study population

The study represents a secondary analysis of EUROASPIRE survey data in the Czech Republic, a prospective follow-up of four pooled independent cohorts (EUROASPIRE I, II, III, and IV examined in 1995–96, 1999–2000, 2006–7 and 2012–13) of patients with stable manifest CHD (i.e. baseline examination was done at least 6 months after its first manifestation). A detailed sample selection was described elsewhere [4,8–10]. Briefly, patients aged less than 71 years hospitalized for any of the following discharge diagnosis were retrospectively identified from hospital records. The diagnoses included: first coronary artery bypass grafting (CABG), first percutaneous transluminal coronary angioplasty (PTCA) and acute myocardial infarction or ischemia. Recruitment of patients started with the most recent hospital record and proceeded backward until the required sample of 525 subjects in each campaign (EUROASPIRE I, II, III, and IV) was achieved. These patients were invited for an interview/clinical examination and responders (81.8% of the initially identified pool of patients) included in the survey. All 4 campaigns of the EUROASPIRE survey were conducted in the same two centers in the Czech Republic: University Hospital in Pilsen and Department of Cardiology, Institute for Clinical and Experimental Medicine in Prague under an almost identical protocol. Each interview/clinical examination took place 6–24 months after the qualifying index event (i.e., acute coronary syndrome or first elective revascularization) and for the purpose of the present analysis used as baseline visit for prospective follow-up.

2.2. Data collection

The standard protocol of EUROASPIRE (EA) survey was followed as described elsewhere [4,8–10]. Briefly, the responders were interviewed at least 6 months after their index event (acute coronary syndrome or first elective revascularization). Information on personal and demographic characteristics, personal and family history of CHD, lifestyle and pharmacotherapy were obtained. The following standardized examinations were performed: height and weight were measured in light indoor clothes without shoes using SECA 707 (EAI and II) and SECA 701 (EA III and IV) scales and measuring stick (SECA, Hamburg, Germany). The scales were calibrated at the start of each survey. Waist circumference was measured using a tape measure. Blood pressure (BP) was measured twice in the sitting position on the right arm using standard mercury sphygmomanometers. Breath carbon monoxide was measured by a SMOKERLYSER device (Bedfont Scientific, Upchurch, UK) to verify smoking status (with 10 ppm of breath carbon monoxide as the cut-off point). Venous blood samples were drawn after at least 12 h of overnight fast. Laboratory examinations included estimation of total and HDL cholesterol, triglycerides (TG) and glucose, and were performed in the central study laboratory of the respective EUROASPIRE survey. Again, laboratory methods were described elsewhere [4,8–10] and comparability of laboratory parameters of both surveys was validated using repeated analyses of long stored frozen samples. LDL cholesterol was calculated using the Friedewald equation, i.e., LDL = total cholesterol − HDL − (TG/2.22).

Vital status of patients was registered up to December 31, 2016 using the National Registry of the Institute of Health Information and Statistics of the Ministry of Health. Death certificates and available documentation in hospital information systems were used to specify the cause of death.

2.3. Outcomes and data management

Primary outcome was defined as death from any cardiovascular cause as stated in hospital records (discharge letter, inspection list, etc.) or, if not available (for those dying at home) stated as the primary cause of death (ICD-10 codes were used) in the death certificate. In patients with active malignancy, the cause of death was considered non-cardiovascular, even if the immediate cause of death was cardiovascular (for example, pulmonary embolism).

Metabolic syndrome (as primary exposure) was identified using four different definitions:

a) standard ("harmonized") ATP definition [3]: presence of at least three of the following factors: "increased waist circumference" (≥102 cm in males or ≥88 cm in females); "raised blood pressure" (systolic BP ≥ 130 and/or diastolic BP) ≥ 85 mmHg)); "low HDL" (<1.0 mmol/L in males or <1.3 mmol/L in females); "hypertriglyceridemia" (fasting TG ≥ 1.7 mmol/L); "increased fasting glycemia" (≥5.6 mmol/L and/or use of antidiabetic treatment); b) modified ATP definition, i.e., similar to the standard definition one, with the exception that current antihypertensive treatment was not used as an alternative criterion for "raised blood pressure";

c) presence of "hypertriceridemic waist" [5] defined as fasting TG ≥ 2.0 mmol/L *plus* waist circumference ≥ 90 cm in males *or* ≥85 cm in females;

d) presence of "atherogenic dyslipidemia" [6] defined as fasting TG ≥ 1.7 mmol/L *plus* HDL < 1.0 mmol/L in males *or* < 1.2 mmol/L in females.

"Overt diabetes mellitus" was defined as fasting glycemia ≥ 7 mmol/L or use of antidiabetic treatment while other conventional risk factors were dichotomized using cut-off points proposed by the Joint European Guidelines for Cardiovascular Prevention [11].

Statistical analyses were performed using STATISTICA 8 (StatSoft Inc., Tulsa, OK, USA) and STATA 8 (STATA Corp LP, College Station, TX, USA). Conventional descriptive methods were applied, i.e., mean and standard deviation for continuous variables or frequency for categorical ones. Using a Cox proportional hazard model, univariate analysis was performed to identify the crude relation between exposure (metabolic syndrome by four different definitions) and cardiovascular mortality. As a second step, we adjusted all models for conventional confounders (age and gender), other (dichotomized) cardiovascular risk factors (smoking, body mass index, blood pressure, LDL cholesterol), treatments with a presumable effect on cardiovascular mortality (statin, beta-blockers,

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