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The relationship of three common definitions of the metabolic syndrome with sub-clinical carotid atherosclerosis

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Abstract

Background: Presence of the metabolic syndrome (MetS) increases a patient's risk for future cardiovascular disease. However, there is no consensus as to which of the proposed definitions should be used. Therefore, using carotid atherosclerotic burden as an index of cumulative effects of atherosclerotic risk factors, we assessed the association of the three commonly used MetS definitions with sub-clinical atherosclerosis in a primary prevention population and determined if this association was independent of the component risk factors.

Methods and results: A multi-ethnic cohort of 796 men and women without cardiovascular disease was assessed for demographics, risk factors, properties of the carotid arteries using ultrasound and presence or absence of MetS based on each of the World Health Organization (WHO), the National Cholesterol Education Program Expert Panel (NCEP) and the International Diabetes Federation (IDF) definitions. Using any definition, 29% of the cohort had MetS. After adjusting for age, gender, ethnicity and smoking status, participants with MetS had greater intima-media thickening and total area (intima-media area and focal lesion area combined) than participants without MetS. Only participants meeting the WHO MetS criteria had a greater prevalence of focal lesions. After further adjustment for the individual risk factor components of each MetS definition separately, none of MetS definitions was associated with any of the carotid artery measures.

Conclusions: All three MetS definitions were associated with measures of sub-clinical carotid atherosclerosis and these associations were entirely mediated through the risk factor components of MetS.

Keywords: Carotid atherosclerosis; Metabolic syndrome; WHO; IDF; NCEP

1. Introduction

The metabolic syndrome (MetS) is defined as a clustering of risk factors for cardiovascular disease (CVD), including abdominal obesity, dyslipidemia, hypertension and insulin resistance [1]. Individuals with MetS are more likely to develop sub-clinical atherosclerosis, CVD and type 2 diabetes, and have greater CVD mortality rates than individuals without MetS [2–9]. Central obesity and insulin resistance are considered to be the principal underlying components in the development of MetS [1,10]. Insulin resistance can lead to metabolic changes, endothelial dysfunction, intima-media thickening (IMT) and later to macro- and micro-vascular complications [5,11–16]. Individuals with MetS have significantly greater IMT values compared to individuals without MetS [3,6,17], and the IMT increases with each additional component of MetS [3].

There are currently three common definitions of MetS: the World Health Organization (WHO) [18], the National Cholesterol Education Program Expert Panel (NCEP) [19] and the International Diabetes Federation (IDF) [20]. These definitions are in general agreement on the essential components of MetS, but differ in their cut-offs and methods of combining the individual components. The WHO focuses

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on diabetes and insulin resistance, and thus an indicator of abnormal glucose metabolism is required, while the NCEP focuses equally on all components, and the IDF focuses on central obesity and has ethnic specific waist circumference (WC) criteria. It is unclear which of these definitions is clinically superior to the others. Depending on the study, IMT is greatest in individuals with IDF MetS [17], while others report individuals with WHO MetS have the highest IMT values [6]. As a predictor of future CVD events, Saely et al. found the NCEP definition to be superior to the IDF definition [7], while both NCEP and WHO were found to be predictive of CVD events [8]. In individuals with diabetes, NCEP and WHO MetS were both predictive of events, whereas IDF was not [21,22]. Two additional studies found all three definitions to be predictive [23,24]. These different findings may be due to differences in study populations such as ethnicity (i.e.: Asian compared to Caucasian), presence of diabetes, and/or suspected CVD. As a result of this conflicting evidence, the medical community has yet to come to a consensus on which definition to use in clinical practice.

As individuals presenting with classical CVD risk factors and/or diabetes should be aggressively treated, the diagnosis of MetS in these patients may not serve additional purpose [25]. Therefore, earlier studies in individuals with diabetes and/or suspected CVD may not be clinically relevant. The potential clinical benefit of the MetS diagnosis is the ability to identify individuals who do not have overt disease or risk factors, but who may be at greater risk than others, and consequently to provide appropriate treatment. However, if the diagnosis of MetS does not provide any additional predictive value over and above the measurement of its individual components, then its clinical utility may be questioned. The purpose of this study was to compare the association of the three commonly used MetS definitions with sub-clinical carotid atherosclerotic measures (an index of cumulative effects of atherosclerotic risk factors), and to determine if the association of MetS is independent of the component risk factors in a primary prevention population.

2. Methods

2.1. Study subjects

Participants from the Multi-Cultural Community Health Assessment Trial (M-CHAT) were used in the present investigation [26]. The M-CHAT study consists of a multi-ethnic cohort of apparently healthy men and women (30 to 65 years of age) equally distributed across ethnicity (Aboriginal, Chinese, European and South Asian) and BMI range (18.5–25, 25–30, >30 kg/m^2). Individuals who had recent weight change (>2.2 kg in 3 months) [27], a previous diagnosis of Type 1 or 2 diabetes mellitus, CVD or significant co-morbidity (i.e. HIV, immuno-compromised condition) based on self-report, were currently taking medications for CVD risk factors (i.e. lipid-lowering, anti-hypertensive or hypoglycemic medications), or had significant prosthetics or amputations were excluded. A total of 829 participants were recruited but only participants who had all measures assessed were included in this investigation ($n = 796$). All participants provided informed consent and this study was approved by the Simon Fraser University Research Ethic Board.

2.2. Anthropometric measures

Participants were assessed for socio-demographics, medical history, family history of CVD and type 2 diabetes mellitus (occurrence in parents or siblings at any age) using a standardized interview. Body mass index was calculated from weight (kg) and height (m) in light clothing and with no footwear. Waist circumference was taken at the narrowest location from the anterior view. Hip circumference was taken at the greatest gluteal protuberance. Waist to hip ratio (WHR) was calculated by dividing waist by hip circumference.

2.3. Metabolic risk factors and metabolic syndrome

Fasting blood samples were collected and immediately processed for total cholesterol, HDL-C, triglycerides, apolipoprotein B (apo B), C-reactive protein (CRP), fibrinogen, glucose and insulin. All measurements were carried out in the same clinical laboratory using standard enzymatic procedures. LDL-C was calculated using the Friedewald equation [28]. Blood pressure (BP) was recorded as the average of five successive measurements following ten minutes of seated rest using an automated oscillometric office BP monitor (VSM MedTech Ltd. Coquitlam, British Columbia). Participants were diagnosed for the MetS using the WHO [18], NCEP (glucose threshold $\geq$6.1 mmol/L) [19] and IDF definitions [20]. As this was a multi-ethnic population, the appropriate IDF ethnic cut-offs for WC were used.

2.4. Carotid ultrasound

Carotid artery ultrasound scans were recorded for each participant using a 10 MHz linear array transducer, as previously described [29,30]. The IMT was assessed by measuring over a uniform length of 10 mm in the far wall of the right and left common carotid arteries, within 2 cm proximal to the carotid bulb. The region with the thickest IMT, excluding areas with focal lesions, was measured and the average from the right and left IMT measures was used. Focal lesions were defined as any focal protrusion that was increased compared to the surrounding IMT. This method does not require a minimum threshold for lesion determination and considers all focal protrusions within the carotid tree (common, internal, external carotid arteries and bulb). This differentiation between diffuse thickening and focal protrusion is made to reflect the different pathological processes involved in artery wall thickening and plaque formation [31]. While the prevalence of measurable lesions exceeded 50%, only three were considered hemodynamically significant. The area of each