Atherosclerosis 211 (2010) 612–617

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Association between metabolic syndrome or its components and asymptomatic cardiovascular disease in the RIVANA-study

M.J. Guembe[a,*], E. Toledo[b,c], J. Barba[d], E. Martínez-Vila[e], P. González-Diego[f], P. Irimia[e], J. Díez[g], J.J. Viñes[a]

[a] Department of Health Education and Development, Department of Health, Government of Navarra, Pamplona (Navarra), Spain
[b] Dept. of Preventive Medicine and Quality Management, Hospital Virgen del Camino, Pamplona (Navarra), Spain
[c] Dept. of Preventive Medicine and Public Health, University of Navarra, Pamplona (Navarra), Spain
[d] Dept. of Cardiology, Clínica Universidad de Navarra, University of Navarra, Pamplona (Navarra), Spain
[e] Dept. of Neurology, Clínica Universidad de Navarra, University of Navarra, Pamplona (Navarra), Spain
[f] Dept. of Preventive Medicine and Quality Management, Hospital Garcia Orcoyen, Estella (Navarra), Spain
[g] Department of Cardiology and Cardiovascular Surgery, Molecular Cardiology Unit, Clínica Universidad de Navarra, University of Navarra, Pamplona (Navarra), Spain

ARTICLE INFO

Article history:
Received 13 August 2009
Received in revised form 27 February 2010
Accepted 1 March 2010
Available online 9 March 2010

Keywords:
Metabolic syndrome
Asymptomatic cardiovascular disease
Left ventricular hypertrophy
Carotid intima–media thickness
Microalbuminuria
Atherosclerosis

ABSTRACT

Objective: To assess the association between the metabolic syndrome (MetSd) and asymptomatic cardiovascular disease and determine if the MetSd or its single risk factors perform better in discriminating prevalent asymptomatic cardiovascular disease.
Methods: A total of 880 community-dwelling subjects (423 with and 457 without MetSd according to ATPIII) underwent a physical examination, an echocardiography and an ultrasound examination of carotid arteries and blood and urine samples were collected. Associations between the subclinical organ damage markers and the MetSd were addressed with non-conditional logistic regression. AUCs of ROCs were used to compare the models' ability to discriminate asymptomatic cardiovascular disease.
Results: The MetSd was independently associated with carotid subclinical atherosclerosis, increased left ventricular mass index and cardiac dysfunction. The MetSd did not discriminate prevalent increased carotid intima–media thickness better than abdominal obesity and impaired fasting glucose [AUC = 0.75 (95% CI: 0.71–0.78) and 0.75 (0.71–0.79), respectively; $p = 0.55$]. The MetSd performed worse than abdominal obesity in discriminating increased left ventricular mass index among males younger than 65 years [AUC = 0.66 (95% CI: 0.62–0.69) and 0.69 (0.66–0.73), respectively; $p = 0.02$]. No differences between the ability of MetSd or its components in discriminating increased left ventricular mass index were observed among older men or women. The discrimination ability for microalbuminuria for the MetSd or impaired fasting glucose was not statistically different [AUC = 0.67 (95% CI: 0.60–0.74) and 0.69 (0.62–0.76), respectively; $p = 0.18$].
Conclusion: This study supports the association between the MetSd and asymptomatic cardiovascular disease. The construct of the MetSd might not be better than its single components in addressing cardiovascular risk.

1. Introduction

The association between obesity, hyperinsulinemia, glucose intolerance and dyslipidemia was initially named *Syndrome X* by Reaven. It was not until 1998 that the World Health Organization coined the concept *metabolic syndrome* (MetSd), which has been defined differently afterwards [1]. All various definitions share a common characteristic, namely, they all represent an approach to joining a constellation of different metabolic and anthropometric factors under the same concept, suggesting thus a common underlying condition. In fact, three potential pathogenetic categories of the MetSd have been identified: obesity and adipose tissue disorders, insulin resistance, and several independent factors that mediate specific components of the MetSd, such as molecules of vascular origin.

MetSd has been associated to subclinical atherosclerosis [2,3] and to an increased risk of cardiovascular disease (CVD) or cardiovascular mortality in several studies [4,5]. Moreover, MetSd has also been associated to incident type 2 diabetes mellitus [5]. Although some authors state that the risk for CVD associated with the MetSd

* Corresponding author at: Servicio de Docencia y Desarrollo Sanitarios, Pabellón de Docencia (Recinto Hospital de Navarra), Irunlarrea, 3, 31008 Pamplona, Spain. Tel.: +34 848422006; fax: +34 848422009.
E-mail address: mguembes@cfnavarra.es (M.J. Guembe).

0021-9150/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.atherosclerosis.2010.03.004

is greater than the sum of its risk factors [6,7], evidence is inconsistent [8–10]. In fact, recent studies have shown that the assessment of individual components of the MetSd is more accurate in predicting atherosclerosis progression and CVD mortality than the MetSd itself [11–13].

The aim of this study was to assess the association between the MetSd and asymptomatic CVD and to determine if the MetSd or its single risk factors perform better in discriminating the presence of asymptomatic CVD.

2. Methods

2.1. Study population

The present study is included in the Risk of Vascular Disease in Navarra (Riesgo Vascular en Navarra, *RIVANA*)-Study [14]. The *RIVANA* study was designed to evaluate the prevalence of vascular risk factors and MetSd in the Spanish province of Navarra, their association with asymptomatic CVD, and their impact on vascular disease at ten-years of follow-up. Briefly, 5682 subjects between 35–84 years were selected randomly from the electoral registry of Navarra. Among them, the response rate was 73.4%, resulting in a final sample of 4168 people. A subsample of 1100 participants aged 45–74 years—550 with MetSd according to the ATP III criteria [1] and 550 randomly selected subjects free of MetSd, all of them free of CVD at baseline—were selected to constitute a cohort to address the association between MetSd, asymptomatic CVD and vascular risk. This sample size was calculated based on a 1:1 exposed to non-exposed ratio, a cumulative incidence of 0.045–0.05 for cardiovascular event, an estimated hazard ratio of 2 for MetSd, a statistical power of 80% and an *a priori* defined alpha error of 0.05. Sample size was overestimated an additional 10%. Finally, 521 subjects with MetSd and 533 without MetSd were contacted. Of these, 435 subjects with MetSd and 465 subjects free of MetSd were recruited. Thus, the global response rate was 0.85. Participants were interviewed and examined from June 2004 to June 2008. The present study represents an initial cross sectional analysis of this cohort.

Of the 900 participating subjects, 20 were excluded due to baseline atrial fibrillation or other cardiopathological stages unknown to the participant prior to the baseline examination. Thus, the effective sample size for our analyses was 880 participants (423 with MetSd and 457 free of MetSd).

All participants gave their informed consent and the study protocol was approved by the Institutional Review Board of the Government of Navarra.

2.2. Metabolic syndrome ascertainment

Subjects were classified according to the 2001 ATPIII definition of the MetSd [1] (at least 3 of the following: waist circumference >102 cm in men or 88 cm in women; tryglicerides ≥150 mg/dL or treatment with a LDL-lowering drug; HDL-cholesterol <40 mg/dL in men or 50 mg/dL in women; systolic or diastolic blood pressure ≥130 or 85 mm Hg, respectively, or treatment with blood pressure-lowering drugs; fasting glucose ≥110 mg/dL or prescribed treatment for established diabetes).

2.3. Assessment of asymptomatic CVD

2.3.1. Echocardiography

At baseline, all participants underwent targeted M-mode recordings, two-dimensional imaging and Doppler ultrasound measurements (*Phillips* 7500, Andover, Massachusetts) according to published standards [15]. In the echocardiography, ejection fraction (EF), mitral inflow pattern (*E*/*A*)–defined as the coefficient between peak early filling velocity to velocity at atrial contraction, Doppler tissue velocity of mitral annular motion (*E*) and *E*/*E*′ ratio–defined as the coefficient between the peak early mitral inflow filling velocity and the velocity of mitral annulus early diastolic motion-, isovolumetric relaxation time, mitral valve deceleration time and left ventricular mass to height to the 2.7 power [16] were determined. Low *E*/*A* coefficient was defined as *E*/*A* coefficient <0.75 [17], increased *E*/*E*′ coefficient as *E*/*E*′ coefficient ≥10[17], increased mitral valve deceleration time as mitral valve deceleration time >220 ms [18] and increase isovolumetric relaxation time as isovolumetric relaxation time >100 ms [18]. A left ventricle mass index above 52 g/m$^{2.7}$ for men and above 41 g/m$^{2.7}$ for women was considered as increased [19]. Systolic dysfunction was defined by an ejection fraction smaller than 0.50.

All echocardiographies were done by the same trained cardiologist.

2.3.2. Ultrasound examination of the carotid arteries

Ultrasound examination was performed using high-resolution colour duplex equipment (ATL 1500 HDI) and a linear transducer with a frequency of 5–12 MHz. Intima–media thickness was examined in a standard way in each subject, 1 cm proximal to the carotid bulb in the far wall, with an automated edge detection system developed for that purpose (M'Ath® Std.). Intima–media thickness was defined as the distance between the lumen–intima interface and the media–adventitia interface [20] and an intima–media thickness ≥0.9 mm was considered as increased [21]. Plaques were defined as focal structures encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding intima–media thickness value, or as focal thickening of the intima–media thickness measuring more than 1.5 mm according to the Mannheim carotid intima–media thickness consensus [22]. The presence of atheroma plaques was defined as the observation of plaques at any supraaortic vessel.

Ultrasound examinations were carried out by one certified sonographer blinded to the participants' clinical information, specially trained in carotid intima–media thickness measurements.

2.3.3. Renal function assessment

From each participant, a fasting blood sample and a urine sample were obtained. In the fasting blood sample, plasma creatinine was measured. Glomerular filtration rate was appraised by the MDRD-4 (Modification of Diet in Renal Disease) equation [23].

In the urine sample, proteinuria and albuminuria were assessed with kinetic nephelometry. Subclinical nephropathy was defined by the presence of microalbunimuria (≥30 to <300 mg/dl), low glomerular filtration rate (<60 ml/min) and light increase in serum creatinine (1.3–1.5 mg/dl in men and 1.2–1.4 mg/dl in women). Renal disease was defined as presence of proteinuria (≥300 mg/dl) or increased serum creatinine (≥1.5 mg/dl for men or ≥1.4 mg/dl for women).

2.4. Physical examination and determination of biological parameters

Finally, in the physical examination, waist circumference, height, weight and blood pressure of all participants were registered. Body-mass index was calculated as the weight divided by the square of the height (kg/m^2) and categorized into normal weight (<25 kg/m^2), overweight (25 to <30 kg/m^2) and obesity (≥30 kg/m^2).

In the fasting blood sample, fasting glucose, insulin, HDL-cholesterol, plasma triglycerides and specific C reactive protein of high sensibility were ascertained. Specific C reactive protein of high sensitivity greater than 0.3 mg/dl was defined as high [24].