Atherosclerosis 235 (2014) 538–545

Contents lists available at ScienceDirect

Atherosclerosis

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

Insulin resistance and systemic inflammation, but not metabolic syndrome phenotype, predict 9 years mortality in older adults

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ARTICLE INFO

Article history:
Received 2 February 2014
Received in revised form
28 May 2014
Accepted 29 May 2014
Available online 10 June 2014

Keywords:
Insulin resistance
C reactive protein
Mortality
Metabolic syndrome
Elderly

ABSTRACT

Background: Although metabolic syndrome (MS) is a typical condition of middle-aged/older person, the association between MS and mortality risk has not been confirmed in people over 65 years. We hypothesized that while in the elderly MS phenotype might lose its value in predicting mortality risk, the two core factors of MS, i.e. insulin resistance (IR) and low grade systemic inflammation (LGSI) would not.
Methods: 1011 community-dwelling older individuals (InCHIANTI study) were included. MS phenotype was defined by NCEP-ATP-III criteria. IR was calculated by HOMA; high-sensitivity C reactive protein was measured by ELISA. Subjects were divided into four groups based on presence/absence of IR (HOMA $\geq$ 2.27) and LGSI (hs-CRP $\geq$ 3 g/L): Group 1: no IR/LGSI (reference); Group 2: LGSI only; Group 3: IR only; Group 4: IR + LGSI. Hazard Ratios (HR) for 9-years cardiovascular (CVD) and total mortality, according to IR/LGSI groups, were estimated in subjects with (n.311) and without MS by Cox model.
Results: 31.8% of subjects with MS phenotype had no IR, 45.3% had no LGSI; moreover, 51% of subjects with both IR and LGSI didn't display the MS phenotype. MS phenotype was not associated with CVD (HR: 1.29; 95%C.I.:0.92–1.81) or total (HR: 1.07; 95%C.I.:0.86–1.34) mortality risk, whereas the presence of IR plus LGSI was associated with increased CVD (no MS: HR 2.07, 95%CI: 1.12–3.72; MS: HR 9.88, 95%CI: 2.18–4), and overall (no MS: HR 1.72, 95%CI: 1.001–3.17; MS: HR 1.51, 95%CI: 1.02–2.28) mortality risk. The presence of IR (HR: 6.90, 95%CI: 1.45–32) or LGSI (HR 7.56, 95%CI: 1.63–35) was associated with CVD mortality, only among individuals with MS phenotype.
Conclusions: Among community-dwelling older individuals, IR and LGSI, but not MS phenotype, was associated with 9-years overall and CVD mortality risk. Since a reduced "overlap" between MS phenotype and its physiopathological core (IR and LGSI) might be present with aging, we suggest that the definition of MS might be more holistic in advanced age, and probably comprise the measurement of IR and LGSI.

1. Introduction

Metabolic syndrome (MS) is a phenotype characterized by the clustering of some cardiovascular risk factors including impaired glucose tolerance, central obesity, dyslipidemia, and hypertension [1]. Although the clinical value of diagnosing MS remains still controversial, the role of MS as a possible predictor of cardiovascular disease (CVD), coronary heart disease (CHD), and total

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http://dx.doi.org/10.1016/j.atherosclerosis.2014.05.959
0021-9150/

mortality in adult population has been largely demonstrated [2], also by systematic review and meta-analysis [3].

MS is a condition of middle-aged and older people, as its prevalence progressively increases to a maximum of 25–40% among individuals aged over 70 years [4]. Nevertheless, the association between MS phenotype and mortality has not been consistently confirmed in people over 65 years. Some studies reported a significant association of MS with total [5–7] or CVD mortality [5,8,9] also in older cohorts, while others found no association [10–13]. On the whole, it appears that MS phenotype becomes a weaker predictor of CVD/total mortality in late life, and this concept is supported by studies comparing mortality risk in middle-age versus elderly individuals [12,14].

IR and low grade systemic inflammation (LGSI), two conditions found very often in people with MS, may account for mortality risk associated with MS. IR is widely considered the physiopathological base of MS, and has been associated with increased CVD/total mortality, both in diabetic and non-diabetic individuals [15–18]. LGSI, diagnosed by chronic elevation of C reactive protein (CRP), also seems to play an important role in the development of both IR and MS [19,20]. Interestingly, not only LGSI participates to atherosclerosis process [21,22], but has been also associated with CVD/total mortality both in middle-age [23–25] and older populations [26–28].

We hypothesized that while in the elderly MS phenotype might lose its value in predicting CVD/total mortality risk, the two core factors of MS (i.e. IR and/or LGSI) would not. In order to verify this hypothesis, we investigated the combined effect of IR and LGSI on the risk for 9-years CVD/total mortality in older individuals with and without MS enrolled in the InCHIANTI study.

2. Materials and methods

This study is part of the "Invecchiare in Chianti" (Aging in the Chianti area, InCHIANTI) study, a prospective population-based study of older persons, designed by the Laboratory of Clinical Epidemiology of the Italian National Research Council of Aging (INRCA, Florence, Italy). The study included participants randomly selected from the residents in two towns of the Chianti area. A detailed description of sampling procedure and data collection method has been previously published [29]. Briefly, in 1998, 1270 persons ≥65 years were randomly selected from the population registries. Additional subjects ($n = 29$) were randomly selected to obtain a sample of 30 men and 30 women aged ≥ 90 years old. Of the initial 1299 subjects, 39 were not eligible. Clinical visits and assessments were performed in the study clinic and were preceded by an interview conducted at the participants' homes. Trained interviewers administered structured questionnaires on dietary intakes, household composition, social networks, economical status, education, and general information on health and functional status. The INRCA Ethical Committee ratified the entire study protocol. The analyses presented here are based on data from 1011 individuals aged over 64 in which metabolic parameters and inflammatory mediators had been measured at baseline visit.

2.1. Clinical chemistry parameters

All parameters were measured on fresh serum/plasma drawn after 12 h overnight fasting, after the patient has been sedentary in sitting/supine position for 15 min.

Plasma lipids, fasting glucose and insulin, and high-sensitivity C reactive protein (hs-CRP) were measured as previously described [30]. Cut-off value for LGSI was defined at hs-CRP value ≥3.0 mg/L, as reported in literature [31]. Insulin resistance was calculated according to the Homeostasis Model Assessment (HOMA) as follows: fasting insulin (U/L) × fasting glucose (mmol/L)/22.5.

2.2. Insulin resistance/low grade systemic inflammation (IR/LGSI) classification

Subjects were divided into four groups based on HOMA and hs-CRP values:

• 1: HOMA <2.27 (median value) and hs-CRP <3 mg/L	=no IR, no LGSI **(reference)**
• 2: HOMA <2.27 and hs-CRP ≥3 mg/L	=no IR, LGSI
• 3: HOMA ≥2.27 and hs-CRP <3 mg/L	=IR, no LGSI
• 4: HOMA ≥2.27 and hs-CRP ≥3 mg/L	=IR and LGSI

MS was defined by criteria of the 2005 NCEP-ATP III-AHA/NHLBI statement [32] in the presence of ≥3 of following criteria:

- Waist circumference ≥102 cm in men or ≥88 cm in women
- Triglycerides ≥150 mg/dL or hypertriglyceridemia treatment
- HDL-C <40 mg/dL in men or <50 mg/dL in women or low HDL-C treatment
- Blood pressure ≥130/85 mmHg or hypertension treatment
- Fasting glucose ≥100 mg/dL or hyperglycemia treatment

2.3. Mortality follow-up

Participants were evaluated for the 3-year (2001–2003), 6-year (2004–2006) and 9-year follow-up visits (2007–2009). Mortality data of the original InChianti cohort were collected using data from the Mortality General Registry maintained by the Tuscany Region, and the death certificates that are deposited immediately after death at the Registry office of the municipality of residence. Cardiovascular mortality, based on underlying cause of death, was defined as any cardiovascular mortality and coded using the International Classification of Diseases, 9th Revision (ICD-9 codes: 390-459).

2.4. Other measures

The presence of specific medical conditions was established using standardized criteria combining self-reported history, medical records, and clinical examination. The following diseases were considered: coronary heart disease (CHD-acute myocardial infarction, chronic heart failure, cardiac arrest, acute and chronic ischemic heart disease), peripheral arterial disease (PAD), stroke, hypertension, and diabetes. Prevalent cardiovascular disease (CVD) was defined as the presence of one of the following: CHD, PAD, and stroke. The ankle-brachial index (ABI) was measured in all subjects by using a Doppler stethoscope (Parks model41-A; Parks-Medical Electronics, Inc; Aloha, Oregon). Besides clinical information, the diagnosis of PAD was made If ABI value <0.9.

2.5. Statistical analysis

Continuous variables were expressed as mean (SD) or median (interquartile range) when necessary. Means were compared by ANOVA with Bonferroni post-hoc test for multiple comparison, while medians were compared by Mann–Whitney test. Correlations between continuous variables were tested by Pearson's correlation. Proportion were compared by the χ^2 test. Hazard Ratios