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Association between homocysteinemia and metabolic syndrome in patients with cardiovascular disease

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Background: This is an observational study undertaken in aim to evaluate the association between metabolic syndrome (MS) and high homocysteinemia (HHcy) in relation with cardiovascular disease (CVD).

Methods: The study involved 126 subjects with angiographically documented CVD and 65 healthy subjects. MS has been diagnosed according to the ATP III criteria and plasma homocysteine concentration has been evaluated.

Results: In patients with CVD the prevalence of MS and HHcy is 17.4% and 25.4% respectively; MS coexists with HHcy in 67.2% of patients; analogous results can be observed among men and women. HHcy and MS are associated with CVD (OR 2.53, 95% CI 1.95–12.43 and OR 5.74, 95% CI 2.67–12.34 respectively) but the presence of the two conditions gives rise to a stronger increase in CVD risk (OR 13.11, 95% CI 5.27–32.06).

Conclusions: Our data suggest that HHcy and MS could work together in increasing CVD risk.

Keywords: homocysteine, metabolic syndrome, cardiovascular disease

Introduction

The metabolic syndrome (MS) is characterized by obesity, insulin resistance, hyperlipidemia, and hypertension. The mechanisms causing MS are poorly understood, but insulin resistance is thought to be the major cause (Cranford 2003). Although most people with MS have insulin resistance, which confers increased risk for type 2 diabetes, the primary clinical outcome of this syndrome has viewed as cardiovascular diseases (CVD) (Ninomiya et al 2004). Homocysteine is a sulfur-containing amino acid formed during the metabolism of methionine. In recent years, hyperhomocysteinemia (HHcy) has emerged as an independent and graded risk factor for the development of CVD and it seems that HHcy may specially increase the risk when present with other risk factors for CVD (Virtanen et al 2005). Although HHcy and MS are both associated with CVD, the association between fasting homocysteine levels and MS in CVD patients is not well characterized. This is an observational study undertaken in aim to evaluate the possible association between MS and high homocysteine plasma levels in regard to the risk for CVD.

Subjects and methods

Table 1 shows study subjects characteristics divided in cases and controls; the study involved 126 subjects with angiographically documented CVD, 60 men (age: 34–72 years) and 66 women (age: 36–70 years); angiograms of CAD patients showed at least 50% stenosis of 1, 2, or 3 coronary arteries. 65 aged-matched healthy control subjects were recruited; all were in good general health, had not risk factors for CVD such as smoking, high blood pressure or high cholesterol and triglycerid plasma levels. Patients

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Table 1 Study subject characteristics

	Cases (n = 126)	Controls (n = 65)
Waist circumference (cm)		
Men	109,6 ± 9,8	101,6 ± 8,9
Women	95,2 ± 9,6	88,5 ± 7,4
Triglycerides (mg/dL)	194,3 ± 55,4	147 ± 32,9
HDL-Cholesterol (mg/dL)		
Men	39,6 ± 8,3	43,7 ± 7,4
Women	42,2 ± 9,6	51,2 ± 12,1
Diastolic pressure (mm Hg)	91,1 ± 12,7	79,7 ± 9,2
Systolic pressure (mm Hg)	140,2 ± 15,8	122,4 ± 10,3
Fasting glucose (mg/dL)	109,7 ± 11,2	99,6 ± 27,1
Homocysteine (μmol/L)	28,4 ± 3,9*	10,15 ± 1,9

Values are expressed as mean value ± standard deviation.

*p < 0.05 in comparison with controls.

affected by type 2 diabetes or smokers were excluded by the study, all were in good general health and not taking lipid-lowering drugs or vitamin B₁₂ and folate supplementation.

MS definition

We applied the condition-specific cut points for the MS from the recent NCEP-ATP III report (Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III) 2001). The five component conditions are: fasting glucose ≥ 100 mg/dL, systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, triglycerides ≥ 150 mg/dL, HDL-C <40 mg/dL in men or <50 mg/dL in women and abdominal obesity defined by waist circumference >102 cm in men or >88 cm in women.

Laboratory methods

In aim to determinate fasting plasma levels of homocysteine, triglycerids, LDL-cholesterol, HDL-cholesterol and glucose, all the blood samples were drawn from the cubital vein between 8.00 a.m. and 9.00 a.m. and stored at -20 °C up to the analysis. Triglycerids, LDL-cholesterol, HDL-cholesterol and glucose concentrations were determined by enzymatic-colorimetric methods using standard kits (SENTINEL diagnostics) and finally the colored-derivatives are photometrically quantified by spectrophotometer. Homocysteine concentration was measured immunochemically by automatic analyzer for biological fluid assay (IMX System, Abbott S.p.A., Roma, Italy) FPIA (Fluorescence Polarization Immuno Assay). HHcy was defined as a fasting plasma homocysteine >15 μmol/L (Malinow et al 1999).

Statistical analysis

Continuous variables are presented as mean values ± standard deviation (SD). Odds ratio and 95% confidence interval (CI) were used to study the association between HHcy, MS and CVD, adjusted for age, sex, LDL cholesterol and smoking habit. Findings were considered statistical significant if p value was ≤0.05. Statistical evaluation of the data was performed using standard statistical software (GraphPad Prism).

Results

22 subjects (17.4%) among cases present HHcy and 32 (25.4%) have MS; MS coexists with HHcy in 72 patients (67.2%) and analogous results can be observed among men and women with CVD. The increase in prevalence observed in the MS + HHcy group in comparison with MS and HHcy groups is statistically significant (p ≤ 0.001). As already known, HHcy and MS are both associated with CVD (OR 2.53, 95% CI 1.95–12.43 and OR 5.74, 95% CI 2.67–12.34 respectively); according with prevalence data, when HHcy is associated with MS the OR for CVD rises to 13.11 (95% CI 5.27–32.06). This result suggests that HHcy is a stronger predictor of CVD when present with MS.

Discussion

In the current study, most of cardiopathic subjects (67.2%) show both MS and HHcy, whereas subjects with high plasma homocysteine levels but without MS are 25.4% and only 17.4% of the patients present MS with normal plasma homocysteine levels. These data suggest that HHcy may participate to the metabolic impairment typically observed in MS. Therefore, our results confirm the well known association between HHcy and CVD (OR 2.53, 95% CI 1.95–12.43), so they indicate the usefulness of including fasting homocysteine determination in the diagnostic panels of CVD patients in order to obtain a better assessment of their cardiovascular risk profile. In addition, the present study suggests that HHcy and MS work together in increasing CVD risk, more than the two entities can do alone (OR 13.11, 95% CI 5.27–32.06). These findings surely advice the need to develop strategies for controlling the MS and its component conditions as well as homocysteine plasma levels. The water-soluble B vitamins (especially folate and cobalamin) have been shown to lower HHcy (Lonn et al 2006), but their role in reducing CVD risk is debated (Bonna et al 2006; Siragusa et al 2007); actually, it seems that vitamin supplementation reduces homocysteine plasma levels but it has no effect on the risk of death from cardiovascular causes. These findings suggest that HHcy

needs some other metabolic impairment, such as metabolic syndrome, to exert its negative effect on cardiovascular risk profile. However, Hajer et al (2007) have recently demonstrated in a large prospective study that the contribution of HHcy to SM in determining cardiovascular risk is only modest and the deleterious effect of HHcy is greater when it is alone than associated with MS.

There is full agreement that therapeutic lifestyle change, with emphasis on weight reduction, constitutes first-line therapy for MS. Recently, it has been demonstrated that physical activity is an independent life-style habit associated with a lower homocysteinemia in an elderly population (Danker et al 2004). In conclusion, our study reaffirms the clinical importance of the HHcy especially in association with MS as significant risk factors for CVD and the need to develop strategies for controlling this syndrome.

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