Nutrition, Metabolism & Cardiovascular Diseases (2011) 21, 651–657

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

Nutrition, Metabolism & Cardiovascular Diseases

Association of plasma markers of cholesterol homeostasis with metabolic syndrome components. A cross-sectional study☆

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Received 29 July 2009; received in revised form 30 December 2009; accepted 5 January 2010

Abbreviations: MetS, metabolic syndrome; EPIC, European prospective investigation into cancer and nutrition; CHD, coronary heart disease; BMI, body mass index; LDL, low-density lipoprotein; HDL, high density lipoprotein; apoE, apolipoprotein E; ATP III, Adult Treatment Panel III; IDF, International Diabetes Federation; OR, odds ratio; ABCG5/8, ATP-binding cassette sub-family G members 5/8; LXR, liver X receptor.

☆ Disclosure statement: the authors have no disclosures.

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doi:10.1016/j.numecd.2010.01.005

KEYWORDS
Cholesterol metabolism;
Metabolic syndrome;
Cardiovascular risk factors;
Adiposity;
Lipids and lipoproteins;
Phytosterols;
Lathosterol

Abstract *Background and aims:* Increased plasma phytosterols, which reflect enhanced cholesterol absorption, have been related to an increased risk of cardiovascular disease (CVD). However, high CVD risk conditions, such as obesity, diabetes and the metabolic syndrome (MetS) have been associated with reduced cholesterol absorption. We investigated associations between plasma noncholesterol sterols and MetS components.
Methods and results: With a cross-sectional design, we related MetS components to plasma noncholesterol sterol-to-cholesterol ratios measured by gas chromatography in 674 dyslipidemic patients and 361 healthy subjects participating in a prospective cohort study.

Plasma phytosterol-to-cholesterol ratios were inversely associated with all components of the MetS. In the dyslipidemic group, multivariable analyses showed that a 1-SD increase in sitosterol-to-cholesterol ratio was associated with a reduced risk for any MetS feature, ranging from 0.57 (95% CI, 0.45 to 0.71) for visceral adiposity to 0.82 (95% CI, 0.69 to 0.98) for high blood pressure. The risk of having MetS was nearly halved, with ORs of 0.49 (95% CI, 0.38 to 0.64) or 0.56 (95% CI, 0.44—0.70), depending on the definition. Results were opposed for plasma lathosterol, a marker of cholesterol synthesis. Most findings were reproduced in the healthy cohort. ApoE genotype was unrelated to plasma noncholesterol sterols.
Conclusion: In both dyslipidemic and healthy populations, MetS is associated with increased plasma lathosterol, a cholesterol synthesis marker, and decreased plasma sitosterol, a marker of cholesterol absorption. Elevated plasma phytosterols related to a lower frequency of cardiometabolic risk factors, suggesting that they are associated with a reduced CVD risk.

Introduction

Dietary sterols consist of animal-derived cholesterol and plant sterols (phytosterols), of which the principal molecular forms are sitosterol and campesterol [1]. These compounds are structurally related to cholesterol, but have bulkier and more hydrophobic molecules, which confer them a higher affinity for intestinal micelles than cholesterol. Consequently, cholesterol is displaced from micelles and the amount available for absorption is limited. The phytosterol content of usual diets is similar to that of cholesterol, but their intestinal absorption is much less efficient [see review [2]]. Because of low absorption and rapid biliary elimination, physiological plasma concentrations of phytosterols are in the order of 10^{-3} those of cholesterol.

The lower absorption of phytosterols compared to cholesterol is attributable to active resecretion back into the intestinal lumen, a process which is mediated by the half-transporters ABCG5 and ABCG8. Genetic defects in these transporters [3] cause sitosterolemia, a rare autosomal recessive disorder characterized by intestinal sterol hyperabsorption, raised plasma phytosterol levels, xanthomas and accelerated atherosclerosis. Because of the presumed pathogenic role of elevated plasma phytosterols in sitosterolemia, the question whether high levels of circulating phytosterols might also be atherogenic in non-sitosterolemic individuals has been much debated [4,5].

The plasma ratios of phytosterols to cholesterol are accepted as surrogate markers for the efficiency of intestinal cholesterol absorption, while those of the cholesterol precursor lathosterol are a reliable index of cholesterol synthesis [6]. A reciprocal relationship exists between cholesterol synthesis and absorption, whereby individuals who synthesize little cholesterol tend to absorb more, while those disclosing high cholesterol synthesis show low absorption rates [7], thus these interrelated regulatory mechanisms contribute to tightly controlling cholesterol homeostasis. It has been known for some time that obesity is associated with markedly increased cholesterol synthesis [8]. More recently, Miettinen and colleagues have shown that obesity and related metabolic disturbances, such as type-2 diabetes, insulin resistance and the metabolic syndrome (MetS), are characterized not only by increased cholesterol synthesis (as determined by raised plasma lathosterol levels) but also by low cholesterol absorption (as determined by decreased plasma phytosterol levels) [9—12]. Other authors have reported similar findings in patients with MetS [13].

The presumed enhanced cardiovascular risk of moderately elevated plasma phytosterol levels [4,5] is counterintuitive with the notion that the opposite situation, namely low plasma phytosterol levels, occurs in the MetS, a cluster of risk factors carrying a high cardiovascular risk [14]. Former studies showing an association of obesity-related metabolic disturbances with low circulating phytosterol levels [9—13] involved small numbers of study subjects. We therefore assessed whether the association between the MetS and the low cholesterol absorption/high cholesterol synthesis trait existed in two independent groups of subjects well phenotyped for cardiovascular risk factors, a group of 674 Lipid Clinic patients and a sample of 361 healthy persons drawn from the Spanish population cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC), a large prospective study in Europe [15].

Methods

Study population

This is a cross-sectional study of two samples, a series of 674 asymptomatic adults with primary lipid disorders attending two Lipid Clinics in Spain and a group of 361