Nutrition, Metabolism & Cardiovascular Diseases (2012) 22, 849–855

available at www.sciencedirect.com

ScienceDirect

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

Nutrition, Metabolism & Cardiovascular Diseases

Naturally-occurring phytosterols in the usual diet influence cholesterol metabolism in healthy subjects

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Received 4 June 2010; received in revised form 11 January 2011; accepted 17 January 2011

KEYWORDS
Phytosterols;
Diet;
Cardiovascular disease;
Intestinal cholesterol absorption;
Sitosterol

Abstract *Background and aims:* Modulation of cholesterol absorption is potentially an effective way of lowering blood cholesterol levels and decreasing inherent cardiovascular risk in the general population. It is well established that cholesterol absorption efficiency can be modified by the intake of foods enriched with gram-doses of phytosterols, but little is known about the effects of phytosterols in the usual diet, even though moderate doses have been reported to affect whole-body cholesterol metabolism. A way to indirectly measure cholesterol synthesis and absorption rates is by quantification of serum non-cholesterol sterols. The aim of this study was to investigate the role of naturally occurring phytosterol intake on cholesterol absorption and serum cholesterol concentrations in a Spanish free-living population.
Methods and results: A total of 85 healthy volunteers were studied regarding their dietary habits (using a validated food frequency questionnaire), lipid profile and surrogate markers of cholesterol metabolism. Subjects were classified into tertiles of total phytosterol intake, and differences in lipid profile and markers of cholesterol metabolism were assessed by multivariate linear regression models adjusted for various confounders. The estimated daily intake of phytosterols and cholesterol was 489 (median) and 513 (mean) mg, respectively. Both serum low-density lipoprotein (LDL)-cholesterol concentration and sitosterol-to-cholesterol ratio adjusted by sitosterol intake (a surrogate marker of intestinal cholesterol absorption) decreased significantly ($p < 0.05$, both) across tertiles of phytosterol intake.

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0939-4753/$ - see front matter
doi:10.1016/j.numecd.2011.01.010

Conclusion: Moderate doses of phytosterols in the habitual diet might have a protective effect on the lipid profile via decreasing cholesterol absorption.

Cardiovascular disease is a major health problem in developed countries, albeit its incidence is relatively lower in the Mediterranean area, which can partly be ascribed to dietary habits [1].

Presently, there is consistent epidemiologic and clinical evidence relating increased serum cholesterol, specifically low-density lipoprotein (LDL) cholesterol, to an enhanced cardiovascular disease risk. In humans, there is a direct correlation between plasma LDL-cholesterol levels and the efficiency of intestinal cholesterol absorption [2]. A reduction of cholesterol absorption produces a state of relative cholesterol deficiency, which stimulates counter-regulatory mechanisms, namely cholesterol biosynthesis and LDL receptor activity, to maintain cholesterol homeostasis, resulting in decreased LDL-cholesterol concentration as the overall effect [3]. Therefore, modulation of cholesterol absorption is, potentially, an effective way of lowering plasma LDL-cholesterol levels in the general population [4].

Phytosterols, structural and functional components of plant cell membranes with a structure similar to cholesterol, are one of the dietary components that have the capacity to render cholesterol absorption inefficient and, consequently, have a potential cholesterol-lowering effect [3,5,6]. In fact, many clinical trials have shown that phytosterols incorporated into various foods at doses of about 2 g day^{-1} consistently reduce LDL-cholesterol levels by nearly 9% on average in human subjects [7]. However, much less is known about the possible benefits of naturally occurring phytosterols in the usual diet. Estimates of daily phytosterol consumption in various populations range from ~160 to 360 mg [3,6], and these figures are two to three- fold higher among subjects with a high intake of vegetable foods, such as vegetarians [5]. The most concentrated sources of these compounds (sitosterol, campesterol and stigmasterol are the predominant forms) are vegetable oils, seeds, nuts and legumes. Fruits, vegetables and cereals are also important because of the large portion sizes that are consumed [8]. That is why the Mediterranean diet, which is rich in plant-based foods, contains large amounts of phytosterols [9].

Traditionally, phytosterols from the habitual diet have not been considered to have any significant effect on the serum cholesterol level, but it has been suggested that the relatively low doses contained in non-supplemented foods influence cholesterol absorption [6]. Moreover, recent epidemiological studies [10,11] have shown that phytosterols from the usual diet relate inversely to serum total and LDL-cholesterol levels, while two recent controlled feeding trials [12,13] have reported that even moderate doses affect whole-body cholesterol metabolism.

Cholesterol synthesis and absorption rates can be indirectly measured by quantification of serum non-cholesterol sterols expressed as ratios to serum cholesterol. The ratios of cholesterol precursors reflect absolute cholesterol synthesis, while those of phytosterols reflect cholesterol absorption efficiency [14]. However, the circulating levels of phytosterols appear to be related to the amount in the diet [14,15]; hence, their reliability as surrogate markers of absorption is questionable when the dietary amounts of phytosterols consumed are different among the subjects studied [16]. In those cases, although cholesterol absorption probably decreases, the serum concentrations of phytosterols actually increase in such a manner that they reflect dietary intake [12,13,17,18].

The aim of the present study was to investigate the role of naturally occurring phytosterol intake from the usual diet on intestinal cholesterol absorption, as determined from serum levels of surrogate markers of absorption, and on the serum lipid profile in a Spanish free-living population.

Methods

Study population

The participants were healthy adults aged 18—66 years from the Aragon region in Northeastern Spain. All of them belong to a hospital and university environment, and were invited by means of advertising campaigns or directly by the researchers. They fulfilled the following criteria: no known cardiovascular disease or secondary hyperlipidaemia; body mass index (BMI) values lower than 30 kg m^{-2} and waist circumference lower than 102 cm (men) or 88 cm (women); no menopausal status in women; and no habitual consumption of phytosterol-supplemented foods. All subjects volunteered to the study and gave written informed consent. The study protocol was approved by the Aragon Ethics Committee of Clinical Investigation.

Medical and lifestyle information and anthropometric measurements

Participants attended an interview with a trained dietitian, who collected demographic data, information on lifestyle factors, including food consumption, smoking and physical activity and a comprehensive medical history, including prior diagnosis of hypertension, hyperlipidaemia or diabetes and medication use. At the same visit, anthropometric measurements (height, weight and waist circumference) were obtained by standard methods. In addition, blood pressure was measured with a validated semiautomatic oscillometer.

Dietary assessment

Information on usual food intake over the previous year was assessed by a 136-item semi-quantitative food frequency questionnaire (FFQ) previously validated in Spain, which properly ranks individuals according to their usual intake [19]. Nutrient scores were calculated as frequency × nutrient composition of specified portion sizes, where