



Increase in HDL-C concentration by a dietary portfolio with soy protein and soluble fiber is associated with the presence of the ABCA1R230C variant in hyperlipidemic Mexican subjects[☆]

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ARTICLE INFO

Article history:

Received 21 June 2010

Received in revised form 3 August 2010

Accepted 3 August 2010

Available online 10 August 2010

Keywords:

Hyperlipidemia

Soy protein

Soluble fiber

Polymorphisms

ABCA1

ABSTRACT

Background: A dietary portfolio has been used to reduce blood lipids in hyperlipidemic subjects. To increase the effectiveness of these dietary treatments in specific populations, it is important to study the genetic variability associated with the development of certain types of hyperlipidemias. Low plasma high-density lipoprotein cholesterol (HDL-C) levels are the most common dyslipidemia in Mexican adults and are coupled with the presence of the ABCA1 R230C genotype. Therefore, the aim of this study was to assess the response of HDL-C concentration to a dietary portfolio in a group of Mexican hyperlipidemic subjects with ABCA1R230C (rs9282541) and R219K (rs2230806) polymorphisms.

Methods: Forty-three hyperlipidemic subjects (20 men and 23 women) were given a low saturated fat (LSF) diet for one month, followed by a LSF diet that included 25 g of soy protein and 15 g of soluble fiber daily for 2 months. We analyzed two ABCA1 polymorphisms and studied their association with serum lipids before and after treatment.

Results: Hyperlipidemic subjects with the ABCA1 R230C genotype showed lower HDL-C concentrations at the beginning of the study and were better responders to the dietary treatment than subjects with the ABCA1 R230R genotype (+4.6% vs. +14.6%) ($p=.05$). According to gender and the presence of the R230C genotype, women responded more significantly to the dietary treatment, reflected by an increase of 21.9% in HDL concentration ($p=.022$), than women with R230R genotype who only experienced an increase of 2.7% in HDL-C concentration. There was no association between the presence of the ABCA1 R219K variant ($p=.544$) and HDL concentration.

Conclusion: Hyperlipidemic Mexican subjects with the ABCA1 R230C genotype showed lower HDL-C concentrations and were better responders to dietary portfolio treatments for increasing HDL-C concentrations than subjects with the R230R genotype.

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1. Introduction

Hypercholesterolemia is a major health problem associated with an increased risk of cardiovascular disease. Several dietary strategies have been used to reduce blood lipids. Previous work has shown the

hypolipidemic effect of a dietary portfolio consisting of a combination of soy protein and soluble fiber integrated with a low saturated fat (LSF) diet in a Mexican group with hyperlipidemia. In that study, 5 SNPs were studied in four genes related to lipid metabolism that included Apo E, ApoA1 and ABCG5/8 that had been associated with different responses to dietary treatments. The results showed a 40% decrease in triglycerides and a 20% decrease in total cholesterol independent of these polymorphisms [1].

However, recent work has shown the susceptibility of Hispanics to metabolic disease related to their Native American heritage. A frequent cholesterol transporter ABCA1 gene variant (R230C) apparently exclusive to Native American individuals was associated with low HDL-C levels [2], obesity and type 2 diabetes in Mexican Mestizos.

Low high-density lipoprotein cholesterol (HDL-C) plasma levels are the most common dyslipidemia in Mexican adults [3]. Decreased levels of HDL-C have been consistently associated with an increased risk of coronary heart disease (CHD) [4]. HDL includes a

Abbreviations: CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; ABCA1, ATP-binding cassette transporter A1; SSF, Dietary treatment with including 25 g of soy protein and 15 g of soluble fiber; LSF, low saturated fat; TC, serum total plasma cholesterol; LDL-C, low-density lipoprotein cholesterol concentration 39.0 ± 1.1 , and serum; TGs, triglycerides; ATPIII, The National Cholesterol Education Program Adult Treatment Panel III; SNPs, Single-nucleotide polymorphism.

[☆] Supported by the Consejo Nacional de Ciencia y Tecnología (CONACyT grant C01-016 (to A.T.) and partially supported by CONACyT 69856 (to SC).

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heterogeneous group of lipoproteins known to have different antiatherogenic properties and the capacity to promote cholesterol efflux from peripheral tissues [4,5]. The ATP-binding cassette transporter A1 (ABCA1) plays a key role in cholesterol efflux and transfer from peripheral cells to lipid-poor Apo A-I, the first step in HDL-C particle formation [6–8]. The effect of ABCA1 genetic polymorphisms on HDL-C levels has been widely documented mainly in adults [9]; specifically, the K allele of the ABCA1 R219K polymorphism has been associated with increased HDL-concentrations [10–13] and a reduced incidence of coronary heart disease (CHD) events [10,11].

The high frequency of the ABCA1 R230C variant in the Mexican population has been suggested as a selective advantage. Thus, those individuals with the R230C variant probably had a selective advantage during periods of famine. However, R230C carriers currently exposed to an obesogenic environment may be prone to the development of diseases grouped under the metabolic syndrome. The thrifty genotype may predispose our population to respond in a different way to changes in lifestyle, including changes in diet, which would imply the need to establish strategies to treat dyslipidemias in subjects who are carriers of R230C variant compared with individuals homozygous for the wild type variant R230R.

Therefore, the aim of this study was to assess the response of HDL-cholesterol concentration to a dietary portfolio consisting of soy protein and soluble fiber in a group of Mexican hyperlipidemic subjects with or without ABCA1(R230C, rs9282541) and R219K (rs2230806) polymorphisms and to evaluate its association with the dietary portfolio in responders and non-responders.

2. Materials and methods

2.1. Study design

The study followed a prospective cohort design. Subjects were instructed to follow a low saturated fat diet (LSF) diet according to the National Cholesterol Education Program Adult Treatment Panel III (ATPIII) for 4 weeks [14] (period 1). After that, dietary vegetable protein was completely replaced by a soy protein beverage (25 g of soy protein and 15 g of soluble fiber) [15,16] and an LSF diet for 2 months (LSF-SSF diet; period 2). Body weight was measured monthly, and blood samples were obtained after a 12-h overnight fast at one-month intervals. For each subject, body weight and height were measured to estimate energy intake for individual diets. During the study, every ten subjects were assigned to one nutritionist for better follow-up.

Subjects had a medical examination each month, and dietary consumption and body weight were assessed by a nutritionist using a 24-h recall record and standard scale. During the protocol, the nutritionist maintained close contact with subjects twice a week by telephone.

2.2. Study population

In the present analysis, the ABCA1 genotype was measured in forty-three hyperlipidemic participants (20 males, and 9 pre- and 14 postmenopausal women) who completed the 3-month dietary protocol of a previous study devised to study the effect of soy protein and soluble fiber on ABCG5/G8, apolipoprotein E and A1[1]. The participants had a mean (\pm SEM) age of 43.8 (9.4) years, a body mass index of 27.4 (4.4) kg/m², serum total plasma cholesterol (TC) concentration of 283.2 \pm 7.6 mg/dl, low-density lipoprotein cholesterol (LDL-C) concentration of 184.2 \pm 8.3 mg/dl, serum high-density lipoprotein cholesterol (HDL-C) concentration of 39.0 \pm 1.1, and serum triglycerides (TG) levels of 299.4 \pm 13.4 at recruitment. The participants had no history of cardiovascular, renal or liver disease, diabetes, or hypertension, had no smoking or non-alcohol consumption history and were not taking hypolipidemic agents. Subjects were also asked to maintain their habitual level of physical activity throughout the study. All subjects were informed about the protocol, and

written informed consent was obtained from the participants. This study protocol was approved by the Committee of Studies in Humans at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.

2.3. Biochemical assays

During each monthly visit, a 5-ml blood sample was obtained after 12 h of fasting. Blood was centrifuged at 400g, and serum was separated and kept at -20°C until analysis. Serum was analyzed for TC, TG, and HDL-C. Total cholesterol and TG were determined enzymatically [17–19] (SERA-PAK Plus, Bayer de México, Mexico City). Serum HDL-C was determined by an immunoassay method [20] (DiaSys Diagnostics Systems GmbH, Holzheim, Germany), and LDL-C was calculated by the method of Friedewald et al [21] [LDL cholesterol = total cholesterol – (triacylglycerols/2.2 + HDL cholesterol)].

2.4. Genotyping

During the first visit, an additional 5-ml blood sample was drawn, and DNA was extracted from leukocytes as described by Miller et al. [22] These two single-nucleotide polymorphisms (SNPs) of the gene ABCA1 (R230C variant (rs9282541) and R219K (rs2230806)) were determined using polymerase chain reaction (PCR)-based TaqMan allele discrimination assays (ABI Prism 7900HT Sequence Detection System; Applied Biosystems, Foster City, CA) [26]. These genotypes were distributed according to the Hardy–Weinberg equilibrium (<http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl>).

2.5. Statistical analyses

The results are expressed as mean \pm SEM. Differences between the basal and final parameters were evaluated by one-way ANOVA and differences between genotypes and percentage change after treatment were tested with an independent sample Student's *t*-test. Allele frequencies were analyzed using a 2 goodness-of-fit test to determine whether the observed values differed from Hardy–Weinberg equilibrium. Differences with $p < .05$ were considered significant for biochemical parameters. Data were analyzed using SPSS for Windows (version 10.00; SPSS Inc, Chicago, Ill).

3. Results

Genotype distribution (wild type allele homozygote, variant heterozygote, variant homozygote) for each polymorphism was as follows: R230C (31, 12, 0) and R219K (19, 21, 3). Allele frequencies (wild-type, variant) were for R230C (75.5%, 24.4%) and R219K (68.6%, 31.4%).

3.1. ABCA1 R230C

Hyperlipidemic subjects with the ABCA1 R230C variant produced an HDL-C percentage change between basal and final concentration significantly higher after the consumption of the dietary treatment ($p = .05$) than subjects with the R230R genotype, Table 1. Interestingly, subjects with the R230C genotype showed lower basal HDL-C concentrations (36.8 \pm 1.3) than subjects with the R230 R (39.9 \pm 1.5) genotype.

Hyperlipidemic subjects with the ABCA1 R230C genotype were better responders to the low saturated fat diet with respect to HDL-C (5% increase) than the wild type genotype subjects (0.65% increase). However the effect of the low saturated fat diet was limited since there was a no further increase in HDL-C after the inclusion of the soy protein and soluble fiber in the diet for one month. The effect of the dietary portfolio was observed after the second month of dietary treatment. The percent change in HDL-C concentration in the wild type genotype after the dietary treatment was +4.6 \pm 2.3%, whereas in subjects with the R230C genotype was +14.6% ($p = .05$) (Fig. 1).

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