Nutrición Hospitalaria

Original / *Otros*

A genetic variant of the CAPN10 gene in Mexican subjects with dyslipidemia is associated with increased HDL-cholesterol concentrations after the consumption of a soy protein and soluble fiber dietary portfolio

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Abstract

Dyslipidemia is a major public health problem, and therefore, it is important to develop dietary strategies to diminish the prevalence of this disorder. It was recently reported that diet may play an important role in triggering insulin resistance by interacting with genetic variants at the *CAPN10* gene locus in patients with metabolic syndrome. Nonetheless, it remains unknown whether genetic variants of genes involved in the development of type 2 diabetes are associated with variations in high-density lipoprotein cholesterol (HDL-C). The study used a single-center, prospective, cohort design. Here, we assessed the effect of four variants of the *CAPN10* gene on HDL-C levels in response to a soy protein and soluble fiber dietary portfolio in subjects with dyslipidemia. In 31 Mexican dyslipidemic individuals, we analyzed four *CAPN10* gene variants (rs5030952, rs2975762, rs3792267, and rs2975760) associated with type 2 diabetes. Subjects with the GG genotype of the rs2975762 variant of the *CAPN10* gene were better responders to dietary intervention, showing increased HDL-C concentrations from the first month of treatment. HDL-C concentrations in participants with the wild type genotype increased by 17.0%, whereas the HDL-C concentration in subjects with the variant genotypes increased by only 3.22% (p = 0.03); the low-density lipoprotein cholesterol levels of GG carriers tended to decrease (-12.6%). These results indicate that Mexican dyslipidemic carriers of the rs2975762-GG genotype are better responders to this dietary intervention.

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Key words: *Calpain-10, polymorphism, dietary portfolio, hypercholesterolemic, dyslipidemia.*

UNA VARIANTE GENÉTICA DEL GEN CAPN10 EN SUJETOS MEXICANOS CON DISLIPIDEMIA SE ASOCIA CON UN AUMENTO DE LAS CONCENTRACIONES DE COLESTEROL HDL DESPUÉS DEL CONSUMO DE UN PORTAFOLIO DIETARIO DE DE SOYA Y FIBRA SOLUBLE

Resumen

Dyslipidemia is a major public health problem, and therefore, it is important to develop dietary strategies to diminish the prevalence of this disorder. It was recently reported that diet may play an important role in triggering insulin resistance by interacting with genetic variants at the *CAPN10* gene locus in patients with metabolic syndrome. Nonetheless, it remains unknown whether genetic variants of genes involved in the development of type 2 diabetes are associated with variations in high-density lipoprotein cholesterol (HDL-C). The study used a single-center, prospective, cohort design. Here, we assessed the effect of four variants of the *CAPN10* gene on HDL-C levels in response to a soy protein and soluble fiber dietary portfolio in subjects with dyslipidemia. In 31 Mexican dyslipidemic individuals, we analyzed four *CAPN10* gene variants (rs5030952, rs2975762, rs3792267, and rs2975760) associated with type 2 diabetes. Subjects with the GG genotype of the rs2975762 variant of the *CAPN10* gene were better responders to dietary intervention, showing increased HDL-C concentrations from the first month of treatment. HDL-C concentrations in participants with the wild type genotype increased by 17.0%, whereas the HDL-C concentration in subjects with the variant genotypes increased by only 3.22% (p = 0.03); the low-density lipoprotein cholesterol levels of GG carriers tended to decrease (-12.6%). These results indicate that Mexican dyslipidemic carriers of the rs2975762-GG genotype are better responders to this dietary intervention.

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Introduction

Dyslipidemia in Mexican adults is most commonly associated with low plasma levels of high-density lipoprotein cholesterol (HDL-C), which is often related to the development of diseases classified as metabolic syndrome (MetS)[1]. The levels of plasma lipids are controlled by multiple pathways and influenced by complex interactions between many different genes and environmental factors such as diet composition[2].

A low saturated fat diet (LSF) in combination with soy protein and soluble fiber can improve the lipid profile of Mexican subjects with hyperlipidemia[3] independent of genetic variants involved in lipid metabolism. Low-density lipoprotein cholesterol (LDL-C) is reported to be positively associated with the risk of myocardial infarction, whereas HDL-C has an inverse association[4]. LDL-C and HDL-C are among the most commonly measured biomarkers of cardiovascular disease risk in clinical medicine[5], and lower levels of HDL-C have been consistently associated with an increased risk of coronary heart disease (CHD)[6]. Recent studies have shown that LSF, in combination with soy protein and soluble fiber, can increase HDL-C levels in the Mexican population with the *ABCA1* (ATP-binding cassette cholesterol transporter A1) R230C variant[7], which appears to be exclusive to Native Americans[8].

Approximately 74% of the Mexican population with MetS has low a HDL-C concentration and a higher predisposition to develop type 2 diabetes *mellitus*[9]. Nonetheless, it is not known whether genetic variants of genes involved in the development of diabetes are associated with low HDL-C.

The Calpain-10 (*CAPN10*) gene is located on chromosome 2q37 and encodes for a cytoplasmic cysteine protease that requires calcium ions for its activity. In mice, *CAPN10* plays an important role in regulating obesity and type 2 diabetes[10]. This gene has attracted considerable attention because of the association between calpain genetic variation and type 2 diabetes in humans[11-13]. *CAPN10* has been associated with various risk factors of MetS, such as elevated body mass index (BMI)[14], plasma cholesterol concentration[15], hypertension [16, 17] and hypertriglyceridemia[18], and plays an important role in insulin resistance[19]. It has been suggested that *CAPN10* facilitates the translocation of insulin-regulated glucose transporter type 4 (*GLUT4*) by the reorganization of the cytoskeleton[20]. Variations in the *CAPN10* gene are associated with elevated triglyceride levels and reduced expression of *CAPN10* in the adipose tissue of obese subjects[18]. Variations in *CAPN10* confer a risk for type 2 diabetes in several populations, including those of Mexican origin[14-17, 21-23].

However, it is not known whether subjects with variants of the *CAPN10* gene would respond to dietary treatments to improve HDL-C levels. Thus, the aim of this study was to analyze the effects of variations in *CAPN10* on HDL-C levels in Mexican adults in response to a dyslipidemia dietary treatment based on a soy protein and soluble fiber dietary portfolio.

Materials and Methods

Study design

The studied population was selected from a previous study[3]. The study used a single-center, prospective, cohort design. Medical examination was performed each month on all subjects. One nutritionist was assigned for the follow-up of every 10 patients. Body weight and height were measured according to standardize methods to calculate the total energy intake for each patient. Patients were given an LSF diet in accordance with the National Cholesterol Education Program Adult Treatment Panel III (ATPIII) for four weeks (Period 1)[5]. For the next two months, patients were instructed to consume an LSF and dietary portfolio consisting of 25 g of soy protein and 15 g of soluble fiber (LSF-SSF diet) (Period 2). Body weight was monitored during the study, and blood samples were collected after a 12-h overnight fasting period once every month for three months. Nutritionists maintained contact with the subjects twice per week and assessed their dietary consumption using the 24-h recall method and a standard scale.

Study population

Thirty-one hyperlipidemic participants (15 males and 16 females) who completed the three-month dietary protocol were included in the study. The participants had no history of cardiovascular, renal, or liver disease, no history of type 2 diabetes or hypertension, had no smoking or alcohol consumption history, and were not taking hypolipidemic agents. Subjects were asked to maintain their habitual level of physical activity throughout the study. All subjects were fully informed of the protocol, and written informed consent was obtained. This study was approved by the Committee of Studies in Humans at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.

Biochemical assays

A 5-ml blood sample was obtained after a 12-h fasting period each month. Blood was centrifuged at 400 x g, and serum was separated and kept at −20 °C until analysis. Serum was analyzed for total cholesterol (TC), triglyceride (TG), and HDL-C. TC and TG were determined using an enzymatic assay (SERA-PAK Plus, Bayer de México, Mexico City). Serum HDL-C was determined using an immunoassay method[24] (DiaSys Diagnostics Systems GmbH, Holzheim, Germany), and LDL-C was calculated using the method

of Friedewald et al.[25]. [LDL- C = TC − (TG / 2.2 + HDL-C)].

Genotyping

During the initial visit, an additional 5-ml blood sample was drawn, and DNA was extracted from leukocytes as described by Miller et al.[26]. The four single-nucleotide polymorphisms (SNPs) of the gene *CAPN10* previously associated with type 2 diabetes (rs5030952, rs2975762, rs3792267, and rs2975760) were determined using polymerase chain reaction (PCR)-based TaqMan allele discrimination assays (ABI Prism 7900HT Sequence Detection System; Applied Biosystems, Foster City, CA)[27]. The rs5030952, rs2975762, and rs3792267 genotypes were distributed according to Hardy-Weinberg equilibrium (http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl), whereas the rs2975760 genotype was not.

Statistical analyses

Descriptive statistical analyses were conducted for all analyzed variables. Continuous variables were expressed as the means ± SEM. Dichotomous variables were expressed as frequencies and percentages. Variable distribution was assessed using the Kolmogorov-Smirnov Z test; variables with a non-normal distribution were log-transformed prior to analysis. Differences between the basal and final parameters were evaluated using one-way analysis of variance (ANOVA), and differences between genotypes and the percentage change after treatment were tested using an independent sample Student's T-test. Allele frequencies were analyzed using a χ^2 goodness-of-fit test to determine whether the observed values differed from Hardy–Weinberg equilibrium. Differences with $p < 0.05$ were considered significant for biochemical parameters. Data were analyzed using SPSS for Windows (version 10.00; SPSS Inc., Chicago, IL). The effect-size correlation was determined using the Cohen´s d calculation; values > 0.67 were considered large effects.

Results

At recruitment, participants had a mean (±SEM) age of 41.8 (1.46) years with a BMI of 27.9 (0.89) kg/m². The mean serum TC, LDL-C, HDL-C, and TG concentrations were 276 (8.6), 176 (9.62), 39.8 (1.3), and 298.8 (15.7) mg/dl, respectively. The genotype distributions (wild-type allele homozygote, variant heterozygote, variant homozygote) for each polymorphism were as follows: rs5030952 (18, 10, 3), rs2975762 (8, 18, 5), rs3792267 (19, 11, 1), and rs2975760 (31, 0, 0). The allele frequencies (wild type, variant) were as follows: rs5030952 (74%, 26%), rs2975762 (65%,

45%), rs3792267 (79%, 21%), and rs2975760 (100%, 0%). The variant rs2975760 was monomorphic in our study population; therefore, it was excluded from the analysis. These four variants have been reported to occur in linkage disequilibrium in various ethnic groups among American Hispanics[28].

CAPN10 variant rs2975762

The percentage change between the basal and final HDL-C levels after the consumption of the dietary treatment was significantly higher in hyperlipidemic subjects with the GG genotype in the rs2975762 variant ($p = 0.03$) than in subjects with the GA and AA genotypes (table I). The subjects with the wild-type genotype were better responders to the LSF diet (1.3% increase in HDL-C) than were the subjects with the polymorphism (0.4% decrease in HDL-C). An effect of the dietary portfolio was observed from the first month of the dietary treatment. The percentage change in HDL-C concentrations in the wild type genotype after the dietary treatment was + 17.0 ± 9.02, whereas in subjects with the variant genotypes, the change was + 3.22 ± 2.13 ($p = 0.03$) (fig. 1). The analysis of the effect size, a measure of the strength of a phenomenon, showed that GG genotype had a large effect on the dietary treatment, with increased HDL-C levels (Cohen's (d) = 2.10, effect size (r) = 0.72)[29]. Although there was no significant interaction between the GG
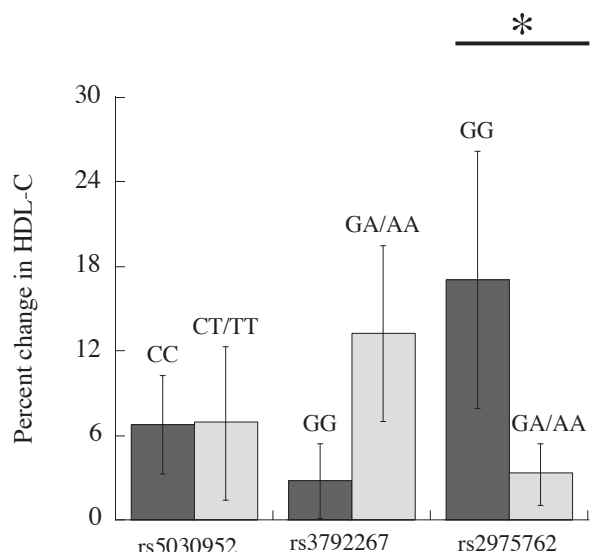

Fig. 1.—*The percentage change in HDL-C concentrations in hyperlipidemic subjects after one month of the low saturated fat diet (LSF) and two months of the LSF diet in addition to 25 g of soy protein and 15 g of soluble fiber (LSF+SSF) divided according to the CAPN10 genotypes. The wild type genotype show the black bars, whereas in subjects with the variant genotypes show the white bars. Values are the means ± SEM. Differences between genotypes and the percentage change after treatment was tested using an independent sample Student´s t-test. *Differences with p < 0.05.*

Tabla I

Serum lipid levels in hyperlipidemic subjects after one month of the LSF diet and after one and two months of the LSF diet in addition to 25 g of soy protein and 15 g of soluble fiber (LSF+SSF). Data are listed according to the CAPN10 genotypes

Genotypes (n)	Basal	1-mo. LSFD	2-mo LSFD + SSF	3-mo LSF + SSF	Percent change after 3 mo. of treatment	P
Total cholesterol (mg/dl)						
rs5030952						
CC (18)	275 ± 12.7[a]	255 ± 13.5[a,b]	229 ± 13.3[a,b]	219 ± 12.7[b]	-20.3 ±2.61	0.432
CT and TT (13)	278 ± 10.9[a]	251 ± 13.6[a,b]	227 ± 7.52[b]	227 ± 5.90[b]	-17.5 ± 2.05	
rs2975762						
GG (8)	251 ± 18.3[a]	212 ± 15.9[a,b]	205 ± 13.8[a,b]	194 ± 14.1[b]	-22.4 ± 3.35	0.269
GA and AA (23)	285 ± 9.25[a]	267 ± 10.2[a,b]	237 ± 9.6[a,b]	232 ± 8.3[b]	-18.0 ± 2.01	
rs3792267						
GG (19)	284 ± 10.8[a]	260 ± 12.5[a,b]	234 ± 10.5[b]	229 ± 9.52[b]	-18.6 ± 2.33	0.726
GA and AA (12)	264 ± 13.9[a]	242 ± 14.8[a,b]	219 ± 13.5[a,b]	212 ± 12.9[b]	-19.9 ± 2.66	
Triglycerides (mg/dl)						
rs5030952						
CC (18)	313 ± 21.4[a]	312 ± 25.5[a]	176 ± 13.8[b]	193 ± 10.5[b]	-33.7 ± 5.25	0.504
CT and TT (13)	279 ±22.0[a]	249 ± 35.8[a,b]	150 ± 19.0[b]	169 ± 26.4[b]	-39.7 ± 7.61	
rs2975762						
GG (8)	288 ± 34.5	280 ± 50.1	171 ± 27.0	179 ± 25.7	-36.8 ± 6.97	0.942
GA and AA (23)	302 ± 17.8[a]	288 ± 23.8[a]	163 ± 12.5[b]	184 ± 14.8[b]	-36.0 ± 5.45	
rs3792267						
GG (19)	284 ±18.9[a]	270 ± 25.8[a]	162 ± 13.4[b]	173 ± 15.6[b]	-35.5 ± 6.25	0.842
GA and AA (12)	321 ± 26.6[a]	310 ± 37.9[a]	168 ± 21.1[b]	198 ± 21.3[b]	-37.3 ± 5.76	
HDL-cholesterol (mg/dl)						
rs5030952						
CC (18)	38.6 ± 1.86	37.8 ± 1.91	40.2 ± 1.82	40.7 ± 1.86	+6.75 ± 3.39	0.985
CT and TT (13)	41.6 ± 1.71	42.7 ± 1.69	42.0 ± 1.89	44.0 ± 2.11	+6.86 ± 5.35	
rs2975762						
GG (8)	37.5 ± 3.29	38.0 ± 3.30	42.3 ± 3.47	43.0 ± 3.58	+17.0 ± 9.02	0.036
GA and AA (23)	40.6 ±1.35	40.5 ± 1.47	40.5 ± 1.33	41.8 ± 1.48	+3.22±2.13	
rs3792267						
GG (19)	41.8 ± 1.82	41.8 ± 1.82	42.4 ± 1.91	42.6 ± 1.79	+2.72 ± 2.56	0.080
GA and AA (12)	36.7 ± 1.42	36.8 ± 1.81	38.7 ± 1.38	41.3 ± 2.35	+13.2 ± 6.12	

Tabla I (cont.)

Tabla I (cont.)

Serum lipid levels in hyperlipidemic subjects after one month of the LSF diet and after one and two months of the LSF diet in addition to 25 g of soy protein and 15 g of soluble fiber (LSF+SSF). Data are listed according to the CAPN10 genotypes

Genotypes (n)		Basal	1-mo. LSFD	2-mo LSFD + SSF	3-mo LSF + SSF	Percent change after 3 mo. of treatment	P
LDL-cholesterol (mg/dl)							
rs5030952	CC (18)	174 ± 14.1	154 ± 14.4	154 ± 14.8	140 ± 14.1	-20.0 ± 4.44	0.498
	CT and TT (13)	180 ± 11.9	158 ± 18.3	155 ± 8.63	149 ± 9.39	-15.5 ± 4.61	
rs2975762	GG (8)	156 ± 18.7	118 ± 15.0	128 ± 17.2	115 ± 17.3	-27.5 ± 5.17	0.084
	GA and AA (23)	184 ± 11.0	169 ± 13.0	163 ± 10.4	154 ± 9.98	-14.9 ± 3.74	
rs3792267	GG (19)	185 ± 12.8	164 ± 15.5	159 ± 11.7	152 ± 11.5	-16.2 ± 4.62	0.464
	GA and AA (12)	163 ± 14.1	143 ± 14.6	147 ± 15.3	130 ± 14.3	-21.2 ± 3.94	

Values are the means ± SEM. Differences between the basal and final parameters were evaluated using a one-way ANOVA, and the differences between genotypes and the percentage change after treatment were tested using an independent sample Student's t-test. Values within a row bearing different superscript letters were significantly different (p< 0.05; a>b>c).

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genotype and dietary treatment affecting the levels of LDL, there was a 12.6% decrease after three months of treatment, and the effect size of the GG genotype was considered to be large (Cohen's (d) = 2.79, effect size (r) = 0.81)[29].

CAPN10 variants rs5030952 and rs3792267

In the rs5030952 and rs3792267 variants, the dietary treatment with soy protein and soluble fiber had no effect on the percentage change in HDL-C concentrations after (HDL P = 0.985, P = 0.080 and LDL P = 0.985, P = 0.464). Despite the lack of a statistically significant difference (P = 0.080), the HDL-C concentrations in subjects with the GA and AA genotypes in rs3792267 increased by 10.48%; the effect size of the GA and AA genotypes on the dietary treatment with respect to HDL-C levels was large (Cohen's (d) = 2.234, effect size (r) = 0.74)[29, 30].

Discussion

Dyslipidemia is a serious public health problem[30], and it is important to develop dietary strategies to diminish its prevalence. This study presents the first report that patients with dyslipidemia and the GG genotype in the rs2975762 gene variant of the *CAPN10* gene were better responders to a dietary intervention consisting of soy protein and soluble fiber, showing increased HDL-C concentrations (17%). In addition, GG carriers showed 12.6% lower levels of LDL-C; the effect size was large despite the lack of a statistically significant interaction. The genotype GG had a beneficial effect on the lipid profile; i.e., the levels of HDL increased significantly, and the levels of LDL tended to decrease. This effect may have been associated with an improved reverse cholesterol transport efficiency and a reduced risk of CHD. However, despite not showing a statistically significant interaction (P = 0.080), subjects with the GA and AA genotypes in rs3792267 showed an HDL-C level increase of 10.48%.

It is well known that HDL-C plasma concentrations can be affected by genetic and environmental factors[31]. For example, it was demonstrated that Mexican hyperlipidemic patients who consumed a dietary portfolio that included a beverage with soy protein (25 g) and soluble fiber (15 g) and presented the R230C genotype in the *ABCA1* gene are better responders to the dietary treatment, showing HDL-C increases of 14.6% and 22% in men and women, respectively[7]. It is important to note that changes in lipids were not related to weight loss because the patients' body weight was not significantly reduced during the present study.

There is evidence that *CAPN10* is a regulator of exocytosis in pancreatic β-cells, and it is believed that an isoform of *CAPN10* senses Ca^{2+} and triggers exocytosis in these cells; furthermore, *CAPN10* protein

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concentrations are correlated with the amount of insulin secreted from β-cells[32]. However, physiologically relevant concentrations of apoA-I and apoA-II (either lipid-free or as a constituent of discoidal reconstituted HDL) significantly increase β-cell insulin secretion, indicating that interventions that increase HDL-C levels may be beneficial in type 2 diabetes treatment[27].

One of the limitations of this study was the small sample size, it is necessary to conduct properly powered prospective studies to determine the interactions between *CAPN10* variation and nutrient intake on serum lipid profiles and other metabolic traits. It will be important to analyze these factors in different ethnic groups. In addition, it will be particularly relevant to analyze variants in the *CAPN10* and *ABCA1* genes together because both genes have shown an association with HDL-C concentrations and dietary intervention in the Mexican population.

In conclusion, nutritional genetic approaches are fundamental for the development of new dietary strategies for target populations. The findings of this study will allow for the development of larger investigations to identify subjects who show different responses to treatment according to their genotypes. Genetic variants of the *CAPN10* gene have been associated with human diabetes and related phenotypes in several populations; however, only a few studies have shown genetic association with lipid metabolism, and the underlying mechanisms responsible for such associations remain poorly understood. The analyzed polymorphisms are intronic, and a functional variant can be in linkage disequilibrium with some of these polymorphisms. By analyzing the *CAPN10* variants in relation to HDL-C concentrations and diet, a high response to dietary treatment on serum lipids can be ensured without exposing the patient to the side effects of medication. In this sense, it is crucial to consider that the cumulative effect of multiple common variants contributes to polygenic diseases such as dyslipidemia[33]. Additional research *in vivo* and *in vitro* with respect to these novel gene-nutrient interactions will help to improve the therapeutic efficacy of dietary interventions using a personalized nutrition approach and aid in the development of population-wide strategies for the prevention of disease.

Acknowledgment

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