A Common Variation in the Caveolin 1 Gene Is Associated with High Serum Triglycerides and Metabolic Syndrome in an Admixed Latin American Population

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Abstract

Background: The caveolin 1 (*CAVI*) gene has been associated with metabolic traits in animal models and human cohorts. Recently, a prevalent variant in *CAVI* has been found to be related to metabolic syndrome in Hispanics living in North America. Since Hispanics represent an admixed population at high risk for cardiovascular diseases, in this study a Latin American population with a similar genetic background was assessed. **Objective:** To analyze a genetic association between *CAVI* and metabolic traits in an admixed Latin American population.

Methods: A cross-sectional study was carried out with adults from the Colombian Caribbean Coast, selected in urban clusters and work places through a stratified sampling to include diverse ages and socioeconomic groups. Blood pressure and waist circumference were registered. Serum concentrations of glucose, triglycerides, and high-density lipoprotein cholesterol were measured from an 8-hr fasting whole-blood sample. Two previously analyzed *CAVI* single nucleotide polymorphisms were genotyped (rs926198 and rs11773845). A logistic regression model was applied to estimate the associations. An admixture adjustment was performed through a Bayesian model.

Results: A total of 605 subjects were included. rs11773845 was associated with hypertriglyceridemia [odds ratio (OR)=1.33, $p=0.001$] and the metabolic syndrome (OR=1.53, $p=0.02$). When admixture adjustment was performed these genetic associations preserved their statistical significance. There were no significant associations between rs926198 and metabolic traits.

Conclusions: The *CAVI* variation rs11773845 was found to be consistently associated with high serum triglycerides and the metabolic syndrome. This is the first report of a relationship between *CAVI* variants and serum triglycerides in Latin America.

Keywords: caveolin 1, metabolic syndrome X, hypertriglyceridemia, genetic association study, Latin America

Introduction

CAVEOLIN 1 IS A ~22 kDa PROTEIN located in plasma membrane invaginations known as caveolae, particular types of cholesterol-rich domains referred to as lipid rafts.¹ Caveolin 1 is encoded by a 36.4 kb gene (*CAVI*) located in chromosome 7 (7q31.1) containing three exons of 30, 165,

and 342 bp, respectively, and two introns that accounts for more than 97% of its total length.^{2–4}

Caveolin 1 assembles in dimeric and oligomeric structures that function as scaffolds to shape the caveolae; therefore, this protein has been designated a molecular marker of this structure.^{5,6}

Caveolae are present in many cellular types, but its presence is notably higher in adipocytes where caveolar

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invaginations represent more than 50% of the external surface.⁷ In fat cells caveolae and caveolin 1 have been found to be co-localized with the insulin receptor, and they interact with insulin receptor-substrate 1 as an enhancing factor.⁸ Furthermore, caveolin 1 and Adiponectin Receptor 1 (Adipor1) shape a signalosome that is associated with insulin sensitivity, lipids, and glucose homeostasis.^{8–11}

In vitro studies have shown that caveolin 1/caveola is associated with lipid bodies, which are the most abundant structures where triacylglycerol molecules are stored in adipocytes.^{12–14} *CAVI* knockout mice develop severe lipodystrophy, and they remain lean after systematic exposition to high-fat diets, in addition to showing energetic metabolism disorders such as insulin resistance and hypertriglyceridemia.^{15–17}

In human populations, genetic variations in *CAVI* have been associated with metabolic disorders and related morbidities (e.g., cardiovascular diseases).^{18–21} In particular, the rs3807989 single nucleotide polymorphism (SNP) has been associated to high serum low-density lipoprotein cholesterol (LDL-C), total serum cholesterol, insulin resistance, and diabetes.^{20,22,23} In addition, rs926198 and rs11773845 SNPs (a proxy for rs3807989) were related with insulin resistance, high blood pressure, diabetes, and metabolic syndrome in populations with European and Hispanic ancestry.^{19,20}

Since the common variant rs926198 located in *CAVI* has been associated with increased risk for metabolic disorders in Hispanic groups,^{19,20} it is plausible that this genetic exposition could be a contributor to the current increase of metabolic disorder incidence in Latin American populations, a recently admixed population with a similar genetic background.²⁴ In fact, the metabolic syndrome prevalence has continuously increased from 20% and 21% in 2008²⁵ to 25% in 2011²⁶ and between 27.5% and 34.1% in 2016.^{27,28} This acceleration in the frequency of metabolic alterations has triggered morbidity and mortality caused by cardiovascular diseases, which represent the leading disability and death among adults.²⁹

In this regard, we have previously found insights about an association between *CAVI*, metabolic traits, and the metabolic syndrome in a sample from Latin America; however, these findings await further confirmation.^{30,31} This work was aimed to determine the association between variants in *CAVI* and metabolic traits in an admixed Latin American population.

Materials and Methods

A cross-sectional study was carried out in Cartagena de Indias, a city of nearly 1 million inhabitants on the Colombian Caribbean Coast.³² Most of the genetics and phenotypic features of the current population are consequence of an intense admixture process that occurred throughout Latin America between the 16th and 19th centuries during Spain's colonial period. According to previous reports, three majoritarian ancestral groups converged in contemporary urban areas: (1) European (60%), (2) African (30%), and (3) Amerindian (10%).³³

For this study, nonsibling adults (18–80 years) living in urban areas were included. To identify possible consanguinity within the subjects, those individuals with similar surnames were contacted by telephone to discard family relations; hence, first and second-degree siblings were ex-

cluded, preserving only one of the subjects for analysis. Individuals with primary endocrine alterations or previous diagnosis of genetic disease were excluded. Subjects with a personal history of surgical treatment for obesity, pregnant women, and breastfeeding mothers were also excluded. All subjects were asked to participate, and their written informed consent was required, following Universidad de Cartagena Ethics Committee recommendations.

Sample size and study power were calculated using the browser program Genetic Power Calculator (<http://zzz.bwh.harvard.edu/gpc/cc2.html>).^{34,35} As parameters, an outcome (metabolic syndrome) prevalence at 33%,³⁶ 25% minor allele frequency (MAF), complete linkage disequilibrium ($D' = 1$), and a 5% alpha coefficient were assumed. Thus, a total sample of 605 subjects was set as the minimum size necessary to achieve 80% power to discriminate genetic associations with a 1.35/1.6 (heterozygote/homozygote) odds ratio (OR).

The study sample was selected through two selection strategies as follows: (1) multistage cluster random sampling and (2) convenience sampling. For the multistage cluster random sampling, city maps were obtained from the local Urban Planning Office. As a first stage, city blocks were identified as primary stage units (PSU) and randomly selected. In a second stage, a group of researchers identified the PSU on the field, and three households were randomly chosen as targets by making a count of the houses, starting at the northern corner and taking three random numbers per block when a complete counting was finished. If at least one adult was present, a list of all the adults was made, and one adult per dwelling was invited to a medical consultation within the next week. This approach has been previously applied by the authors in studies with Caribbean populations.^{36,37}

Since men and groups of employees have been less likely to be included by the cluster sampling method in this population,³⁸ a second strategy was added to reduce selection bias. Hence, a convenience sampling was carried out in workplaces where socioeconomically mixed populations are commonly found, following the methods previously applied in Cartagena de Indias.³¹ Employees were selected from seven work places as follows: (1) a management office, (2) a civil construction company, (3) an industrial production corporation, (4) a security services company, (5) two teaching/learning institutions, and (6) nonprofit humanitarian organization for elderly people and children. Finally, 25% of the total sample was selected with this method.

For both strategies, sample selection was stratified according to the general population age-range distribution as has been described by the *Departamento Administrativo Nacional de Estadística* (National Bureau of Demography and Statistics) and the *Departamento Administrativo Distrital de Salud—Cartagena* (local Public Health Office).^{32,39} The expected distribution is represented in Supplementary Table S1 (Supplementary Data are available online at www.liebertpub.com/met).

Selected subjects were enrolled by a physician and underwent a medical examination that focused on socio-demographic variables and a personal history of metabolic disorders. Anthropometric parameters (height, weight, waist circumference, and hip perimeter) were measured following the International Diabetes Federation guideline, and the blood pressure was recorded by the auscultatory method.^{40,41} A whole-blood sample was collected under 8-hr fasting

conditions to measure the serum concentrations of glucose, triglycerides, and high-density lipoprotein cholesterol (HDL-C), while an aliquot was stored for further genetic analyses. Metabolic syndrome was defined according to Joint Interim Statement criteria.⁴² Body mass index (BMI), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) were also calculated. Body adiposity index (BAI) was determined with the hip perimeter and height values, as was proposed by Bergman et al. (*i.e.*, $BAI = [\text{hip}/\text{height}^{1.5}] - 18$).⁴³

For the genotyping assay, a haplotype of six common variants that covers 80% of *CAVI* genomic region (rs926198, rs11773845, rs3779512, rs10270569, rs7804372, and rs1049337) was identified through Haploview 4.2 software (Broad Institute, Cambridge, MA), using data from CEU populations of the HapMap project ($MAF \geq 0.25$, $r^2 \geq 0.8$). Within these variants, rs926198 and rs11773845 were found to be previously related with metabolic traits and cardiovascular disease and have been identified as a proxy for rs3807989 ($D' = 1$, $r^2 = 1$), another SNP with clinical relevance.^{19,20,44} Hence, both SNPs (rs926198 and rs11773845) were used in further association analysis.

SNPs were genotyped through quantitative polymerase chain reaction (PCR) using specific TaqMan probes (Thermo Fisher Scientific, Inc., Waltham, MA). Allelic discrimination was automatically performed with end point fluorescent data, which were analyzed through StepOne Real-Time PCR Software (Thermo Fisher Scientific, Inc.).

For statistical procedures, sociodemographic data and personal and family antecedents, as well as anthropometric measures and serum concentrations, were described using the main tendency and frequency values. When appropriate, mean values were compared through Student's *t* test, while frequencies were compared with χ^2 or Fisher's exact test. Allelic and genotypic frequencies were determined by direct counting, and linkage disequilibrium was estimated using Arlequin 3.5⁴⁵ and represented as a heat map with R 3.4.2 using the LDheatmap package.⁴⁶ The Hardy-Weinberg Equilibrium was assessed through F_{is} values with Genetix 4.05 software.

To estimate associations between continuous traits and genotype distributions, a Kruskal-Wallis or analysis of variance was performed, while relationships with categorical outcomes were analyzed through a χ^2 test. In addition, recessive and dominant models were assessed using null-hypothesis tests, as has been described elsewhere.⁴⁷

Additive models for genotype-phenotype associations were evaluated through logistic regression, where risk alleles were equal to the unit (risk allele = 1), while anthropometric alterations and metabolic disorders were interpreted as categorical outcomes. This regression model was fitted by age, sex, personal history of diabetes, and BMI. These procedures were performed with R version 3.2.1. and PredictABEL 1.2-2 package.^{48,49} Based on Bonferroni's correction for multiple testing, *P* values < 0.025 were considered statistically significant.

Associations were adjusted by genetic stratification assuming a three-hybrid substructure ($k = 3$), using a Bayesian approach (Markov Chain Monte Carlo, or MCMC) with 100,000 replications through STRAT version 1.1 for DOS/Windows.⁵⁰ The three-hybrid admixture pattern employed was based on previous reports from Cartagena de Indias where Ancestry Informative Markers (AIMs) and Y-Chromosome were used to describe local genetic substructure and ancestry distribution.^{33,51-53} In this study a total of 17 Y-Chromosome Short Tandem Repeats (Y-STR; AmpFLSTR® Yfiler® PCR

Amplification Kit; Thermo Fisher Scientific, Inc.) were used to confirm the admixture in sampled males (data not shown).

Finally, a haplotype analysis for those metabolic outcomes found to be associated with *CAVI* SNPs was performed. Haplotype frequencies were determined, and associations were estimated using a generalized linear regression employing the haplo.stats package for R 3.4.2 software.⁵⁴

Results

A total of 605 subjects were included (59.6% men) at an average 44.7 ± 17.7 years old. Age ranges were distributed according to the population pyramid³⁹: (1) 18–29 years = 24.9%, (2) 30–39 years = 21.1%, (3) 40–49 years = 16.2%, (4) 50–59 years = 14.9%, (5) 60–69 years = 12.1%, (6) 70–79 years = 6.7%, and (7) 80 or more years = 4.1%. The sample socioeconomic distribution was also similar to those proportions described in the general population pyramid (Table 1).³⁹ Estimated income was registered using the national chart of socioeconomic stratification; thus, 74.6% ($n = 451$) met the criteria to be included in the low-income group (*i.e.*, strata 1 and 2), 19.0% ($n = 115$) were included in the middle-income group (*i.e.*, strata 3 and 4), and 2.8% ($n = 17$) were included in the high-income group (*i.e.*, strata 5 and 6), while 3.7% ($n = 22$) did have not enough data to be classified in an economic group.

Regular or occasional alcohol consumption was found in 64.6% ($n = 391$), and 18.5% ($n = 112$) of subjects were identified as active smokers. Regarding family records, participants were asked about metabolic and cardiovascular diseases among known siblings within the last two generations. In this way, 21.5% ($n = 130$) reported at least one dyslipidemia antecedent (*i.e.*, high serum cholesterol, triglycerides, and/or LDL-C), 54.2% ($n = 328$) had at least one known sibling with a clinical history of hypertension, 32.2% ($n = 195$) had family record for type 2 diabetes mellitus, and 39.8% ($n = 241$) reported at least one positive record of cardiovascular diseases defined as coronary artery disease, cardiac arrest, or stroke.

Considering that some common treatments might influence body weight and fat distribution, personal history was focused on the pharmacologic record for metabolic traits. In this sense, the sampled subjects were taking medications for the following: 18.7% ($n = 114$) for dyslipidemia, 26.0% ($n = 159$) for high blood pressure, and 14.9% for diabetes. For dyslipidemia, lovastatin was the most reported drug ($n = 42$), followed by atorvastatin ($n = 16$) and low-lipid diet ($n = 9$). It is noteworthy that among those patients with previous diagnosis of dyslipidemia ($n = 114$), a total of 22 (19.2%) did not remember any detail of their medication (*i.e.*, drug name, doses, and year/date of initiation), and 15 subjects within this group (13.1%) were untreated. For high blood pressure, losartan was found as the most frequent drug ($n = 72$), while hydrochlorothiazide was the second most used ($n = 21$), and amlodipine was the third ($n = 19$). Monotherapy was found in 79 subjects, double therapy in 39 subjects, and triple-drug (or more) therapy was found in 18 subjects. Regarding diabetes, metformin was found to be first-line drug in a total of 36 subjects, while 19 patients were on an insulin-based therapy. In this group, monotherapy was found in 19 subjects, and 15 patients were under a multidrug treatment.

Anthropometric and continuous metabolic traits

As described under the methods, anthropometric variables and blood pressure were measured. The mean value for

TABLE 1. SOCIODEMOGRAPHIC, ANTHROPOMETRIC, AND METABOLIC VARIABLES

	Men	Women	Total	P
n (%)	361 (59.6)	244 (41.4)	605 (100)	
Age (years)	40.1 ± 15.4	48.5 ± 16.1	44.7 ± 17.7	5.58E-10 ^a
Weight (kg)	76.8 ± 14.2	66.7 ± 14.3	72.5 ± 14.8	<2.2E-16 ^a
Height (cm)	171 ± 7.2	158 ± 7.3	166 ± 9.4	<2.2E-16 ^a
Waist circumference (cm)	92.3 ± 10.8	95.2 ± 13.1	93.5 ± 11.2	0.001787 ^a
Hip perimeter (cm)	101.1 ± 9.3	103.3 ± 10.7	102.0 ± 10.0	0.006184 ^a
BMI (kg/m ²)	26.2 ± 4.15	26.6 ± 5.18	26.3 ± 4.62	0.3055 ^a
Waist/hip	0.91 ± 0.06	0.92 ± 0.08	0.92 ± 0.07	0.1496 ^a
Waist/height	54.0 ± 5.94	60.2 ± 8.40	56.7 ± 7.73	<2.2E-16 ^a
BAI ³⁵ (cm/m ^{1.5})	27.2 ± 4.36	34.0 ± 6.13	30.1 ± 6.16	<2.2E-16 ^a
Blood pressure (mmHg)				
Systolic	113.5 ± 14.8	116.3 ± 19.2	114.7 ± 16.9	0.0488 ^a
Diastolic	76.6 ± 10.1	75.1 ± 11.2	75.9 ± 10.6	0.09025 ^a
Serum concentrations (mg/dL)				
Glucose	93.9 ± 27.1	94.8 ± 33.5	94.3 ± 30.0	0.7194 ^a
Cholesterol	184.0 ± 53.2	196.1 ± 57.2	189.2 ± 55.3	0.00802 ^a
Triglycerides	140.0 (106.8–196.0)	133.9 (104.8–178.3)	137.6 (105.4–185.6)	0.09525 ^b
HDL-C	44.1 ± 12.2	49.2 ± 18.0	46.3 ± 15.2	0.0001022

Null hypothesis was carried out to compare groups. Continuous variables are represented as mean ± standard deviation or median (interquartile range).

^at-Student test; ^bMann-Whitney-Wilcoxon test.

BAI, body adiposity index; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol.

weight was 72.5 ± 14.8 kg, while the values for height, waist circumference, and hip perimeter were 166 ± 9.4, 93.5 ± 11.2, and 102.0 ± 10.0 cm, respectively. Blood pressure on average was 114.7 ± 16.9 mmHg (systolic) and 75.9 ± 10.6 mmHg (diastolic). Similarly, averages for BMI, WHR, WHtR, and BAI were 26.3 ± 4.62 kg/m², 0.92 ± 0.07, 56.7 ± 7.7, and 30.1 ± 6.1 cm/m^{1.5}, respectively (Table 1).

The average value for glycemia was 94.3 ± 30.0 mg/dL, for cholesterolemia was 189.2 ± 55.3 mg/dL, the median for triglyceridemia was 137.6 mg/dL insulin resistance (105.4–185.6), and the mean for HDL-C was 46.3 ± 15.2 mg/dL (Table 1).

Frequencies of subjects with overweight and obesity were 41.5% (*n* = 251) and 18.0% (*n* = 109), respectively, while abdominal obesity was found in 71.7% (*n* = 434) of the sampled patients. From the total sample, high-serum glucose was found in 31.7% (*n* = 192), hypercholesterolemia in 30.9% (*n* = 187), hypertriglyceridemia in 41.5% (*n* = 251), hypertension in 29.1% (*n* = 176), and low-HDL-C in 45.8% (*n* = 277) (Table 2). Metabolic syndrome was found in

39.7% (*n* = 240) (Table 2). Within subjects with metabolic syndrome, 63.3% (*n* = 153) met three criteria, 29.5% (*n* = 72) met four criteria, and 7.0% (*n* = 17) met all five criteria.

Association between CAV1 and metabolic disorders

When the genotype analysis was performed, it was found that the MAF (allele C) for rs926198 was 30.4%, with a genotype distribution of 10.1% and 40.8% for CC and CT, respectively (*F*_{is} = 0.03, *p* = 0.19). For rs11773845, MAF (allele C) was equal to 43.5%, with a genotype distribution of 20.7% and 45.6% for CC and AC (*F*_{is} = 0.07, *p* = 0.047).

Mean and median values for continuous traits were compared according to genotype distributions, while dominant and recessive models were assessed. The waist-to-hip ratio was found to be different among rs926198 genotypes (*p* = 0.01) and marginally reduced in the CC+CT model (*p* = 0.05). In addition, rs926198 CC+CT model showed higher systolic and diastolic blood pressure than in the TT group (*p* = 0.02). There

TABLE 2. FREQUENCY FOR METABOLIC TRAITS IN SAMPLE FROM COLOMBIAN CARIBBEAN

	Men, % (n)	Women, % (n)	Total, % (n)	P ^a
Body weight excess				
Overweight	43.8 (158)	38.1 (93)	41.5 (251)	
Obesity	17.2 (62)	19.3 (47)	18.0 (109)	0.3671
Abdominal obesity	61.5 (222)	86.9 (212)	71.7 (434)	2.77E-12
Hypertension	21.3 (77)	40.6 (99)	29.1 (176)	1.04E-10
Hyperglycemia	32.4 (117)	30.7 (75)	31.7 (192)	0.7219
Hypercholesterolemia	26.6 (96)	37.3 (91)	30.9 (187)	0.005529
Hypertriglyceridemia	42.7 (154)	39.8 (97)	41.5 (251)	0.5016
Low serum HDL-C	36.8 (133)	59.0 (144)	45.8 (277)	9.24E-08
Metabolic syndrome	32.7 (118)	50.0 (122)	39.7 (240)	2.24E-05

International Joint Interim criteria were employed to define cutoff point regarding abdominal obesity, hypertension, and high serum concentrations of glucose and triglycerides, as well as low HDL-C.³⁴

^aFisher's exact test.

were no other significant mean or median differences in rs926198 or in rs11773845 (Table 3).

For rs926198 there were significant differences in high serum triglycerides and metabolic syndrome frequencies when TT homozygotes and the CC+CT model were compared ($p < 0.05$). For rs11773845, the differences in high serum triglycerides and metabolic syndrome were also found ($p < 0.05$) (Table 4).

Additive models analyzed through logistic regression revealed associations between rs11773845, hypertriglyceridemia (OR = 1.4, $p = 0.01$), and metabolic syndrome (OR = 1.6, $p = 0.01$). Even when subjects under drug therapy were excluded from study sample, there was found statistically significant association between this SNP and high serum triglycerides (OR = 1.53, $p = 0.01$) (Supplementary Table S2), and metabolic syndrome (OR = 1.54, $p = 0.02$) (Supplementary Table S3). Locus rs926198 showed no significant relationships with any metabolic disorder (Table 5).

Linkage disequilibrium and haplotype analysis

The SNPs rs926198 and rs11773845 were found to be in linkage equilibrium ($r^2 = 0.24$), and there was no linkage disequilibrium between these two loci and other four genotyped SNPs (Supplementary Fig. S1).

Given that high serum triglycerides and metabolic syndrome showed relations in the additive model, the associations with probable haplotypes were estimated. Thus, haplotype T-C (rs926198-rs11773845) was found to be significantly associated with hypertriglyceridemia ($p = 0.004$) and metabolic syndrome ($p = 0.006$) (Table 6).

Discussion

Genetic-association studies focused on metabolic traits have been largely developed in homogeneous populations, mainly in those with European ancestry, but also in groups with Han Chinese, Korean, and Japanese ancestry, among others.^{55–57} Most recently, findings from admixed populations, such as African Americans and Hispanics living in the United States, have revealed autosomal variations linked to obesity, dyslipidemia, diabetes, and cardiovascular diseases.^{58,59} Despite successful findings, the analysis of admixed populations remains a challenging task due to the confounding factors that might lead to spurious associations and false positives, which demand high-powered studies and the application of strict ancestry-adjusted statistical procedures.⁶⁰ Nevertheless, some authors have suggested that genetic features of these populations could be a source of data to identify variations involved in phenotypic diversity commonly found in complex diseases.⁵⁵

Metabolic alterations are well known to cause multiple clinical manifestations and are recognized as main risk factors for cardiovascular disease; however, a large proportion of patients never develop symptomatic pathology, while others suffer severe morbidity. A fraction of that diversity underlies common genetic variations, such as *CAVI* SNPs, which have been found to be prevalent in the general population but with a different distribution among subjects with metabolic disorders and cardiovascular diseases.^{19,20,31,44,61} In the present study an association between a SNP located in *CAVI* (rs11773845), the metabolic syndrome, and high serum triglycerides was found. To the best of our knowledge this is the

TABLE 3. MEAN VALUES FOR ANTHROPOMETRIC AND SERUM BIOCHEMICAL PARAMETERS ACCORDING TO *CAVI* GENOTYPE DISTRIBUTION

	rs926198						rs11773845					
	CC	TC	TT	P	CC+TC	P	TT+TC	P	AA	AC	CC	P
BMI	26.5±4.6	26.2±5.0	26.1±33.1	0.827	26.2±4.9	0.739	26.1±4.6	0.592	26.1±4.3	26.3±4.6	25.9±5.1	0.692
Waist	94.4±10.5	92.2±12.2	93.3±13.5	0.096	92.7±11.9	0.566	93.3±11.1	0.241	93.2±10.4	92.8±10.6	92.8±12.4	0.925
Waist-to-hip ratio	0.93±0.06	0.90±0.07	0.92±0.06	0.01	0.91±0.07	0.050	0.92±0.07	0.139	0.92±0.07	0.91±0.06	0.91±0.07	0.629
Waist-to-height ratio	57.0±7.4	55.8±7.8	56.2±6.8	0.463	56.0±7.8	0.850	56.2±7.3	0.291	56.1±6.6	56.2±7.5	55.9±8.0	0.952
BAI	29.8±5.5	30.0±6.5	29.4±5.1	0.4	30.0±6.3	0.183	29.4±5.8	0.850	29.5±5.5	29.9±5.8	29.6±6.0	0.746
Blood pressure												
Systolic	116±13.4	115.4±17.6	112.4±17.1	0.083	115.5±16.8	0.022	112.4±17.4	0.230	113.3±17.4	113.9±16.1	115.0±18.3	0.69
Diastolic	77.2±11.2	76.3±11.2	74.5±10.2	0.065	76.5±11.2	0.022	74.5±10.7	0.209	74.9±10.5	76.0±10.6	75.5±11.6	0.572
Serum concentrations												
Glucose	93.2±32.6	93.6±29.6	94.9±34.0	0.863	93.5±30.2	0.656	94.9±32.0	0.829	93.8±29.7	94.6±33.8	93.0±31.8	0.901
Cholesterol	182.1±37.6	190.0±54.0	189.3±60.4	0.605	188.4±51.2	0.903	189.3±57.5	0.176	185.2±51.2	192.1±61.9	187.0±48.3	0.394
Triglycerides ^a	132	135.3	139.7	0.686	133.0	0.406	139.7	0.724	147.1	134.9	130.1	0.22
	(110–179)	(103–187)	(106–184)		(103–186)		(104.2–186.4)		(105.4–193.7)	(105.9–181.6)	(103.5–172.6)	
HDL-C	48.2±16.1	46.6±16.0	45.5±14.1	0.384	46.9±16.0	0.212	45.5±15.0	0.306	45.1±13.6	46.3±14.8	47.7±17.6	0.326

Values are represented as mean ± standard deviation.

^aMedian values (interquartile range).

Statistically significant values are highlighted in *bold*.

TABLE 4. FREQUENCIES FOR METABOLIC ALTERATIONS ACCORDING TO CAVI GENOTYPE DISTRIBUTIONS

	rs926198, n (%)					rs1173845, n (%)						
	CC	TC	TT	P	P value (CC+TC v.s. TT)	P value (TT+TC v.s. CC)	AA	AC	CC	P	P value (AA+AC v.s. CC)	P value (CC+AC v.s. AA)
BMI												
Normal weight ^a	22 (36.1)	113 (45.7)	114 (38.4)				84 (41.2)	107 (38.8)	58 (46.4)			
Overweight	26 (42.6)	82 (33.2)	140 (47.1)				88 (43.1)	117 (42.4)	43 (34.4)			
Obesity	13 (21.3)	52 (21.1)	43 (14.5)	0.01486	0.006143	0.6293	32 (15.7)	52 (18.8)	24 (19.2)	0.4455	0.2366	0.5616
Waist circumference												
Abdominal obesity	46 (75.4)	167 (67.6)	221 (74.4)				150 (73.5)	204 (73.9)	80 (64.0)			
No-altered	15 (24.6)	80 (32.4)	76 (25.6)	0.1715	0.1755	0.5517	54 (26.5)	72 (26.1)	45 (36.0)	0.09738	0.03439	0.5051
Blood pressure												
Hypertension	16 (26.2)	82 (33.2)	78 (26.3)				55 (27.0)	86 (31.2)	35 (28.0)			
No-altered	45 (73.8)	165 (66.8)	219 (73.7)	0.1814	0.152	0.6581	149 (73.0)	190 (68.8)	90 (72.0)	0.5789	0.8253	0.4492
Serum glucose												
Hyperglycemia	20 (32.8)	79 (32.0)	93 (31.3)				66 (32.4)	87 (31.5)	39 (31.2)			
No-altered	41 (67.2)	168 (68.0)	204 (68.7)	0.9692	0.8615	0.885	138 (67.6)	189 (68.5)	86 (68.8)	0.9713	0.9145	0.8535
Serum triglycerides												
Hypertriglyceridemia	22 (36.1)	103 (41.7)	126 (42.4)				98 (48.0)	109 (39.5)	44 (35.2)			
No-altered	39 (63.9)	144 (58.3)	171 (57.6)	0.6535	0.007158	0.4122	106 (52.0)	167 (60.5)	81 (64.8)	0.04747	0.1263	0.02319
Serum HDL-C												
Low HDL-C	27 (44.3)	108 (43.7)	142 (47.8)				98 (48.0)	123 (44.6)	56 (44.8)			
No-altered	34 (55.7)	139 (56.3)	155 (52.2)	0.6155	0.3289	0.8924	106 (52.0)	153 (55.4)	69 (55.2)	0.7291	0.8406	0.4384
Metabolic syndrome												
Yes	23 (37.7)	96 (38.9)	121 (40.7)				95 (46.6)	103 (37.3)	42 (33.6)			
No	38 (62.3)	151 (61.1)	176 (59.3)	0.8576	0.0277	0.7839	109 (53.4)	173 (62.7)	83 (66.4)	0.03654	0.1249	0.01405

^aIncludes subjects in under-weight (n=20).
Statistically significant values are highlighted in *bold*.

TABLE 5. ASSOCIATION BETWEEN *CAVI* VARIATIONS AND METABOLIC DISORDERS

	<i>rs926198</i>					<i>rs11773845</i>				
	β -Coefficient	OR	95% CI	P ^a	P value (adjusted) ^b	β -Coefficient	OR	95% CI	P ^a	P value (adjusted) ^b
Weight excess	-0.042	0.95	0.71–1.29	0.779	0.610	0.018	1.01	0.78–1.33	0.894	0.830
Abdominal obesity	-0.078	0.93	0.58–1.47	0.741	0.740	0.251	1.29	0.84–1.96	0.241	0.030
Hypertension	0.070	1.07	0.70–1.66	0.748	0.130	-0.202	0.81	0.54–1.23	0.337	0.940
Hyperglycemia	0.029	1.02	0.76–1.40	0.853	0.920	0.107	1.11	0.83–1.48	0.459	0.930
Hypertriglyceridemia	0.069	1.07	0.79–1.45	0.654	0.310	0.365	1.44	1.08–1.90	0.010	0.010
Low serum HDL-C	-0.106	0.90	0.67–1.21	0.486	0.550	0.072	1.07	0.82–1.41	0.606	0.600
Metabolic syndrome	-0.021	0.97	0.67–1.42	0.912	0.310	0.461	1.58	1.11–2.26	0.011	0.020

An additive model was assessed through a logistic regression where risk alleles were interpreted as the unit. Genetic variations in *rs926198* (TT=0, CT=1, and CC=2) and *rs11773845* (CC=0, AC=1, and AA=2) were included as independent variables. Age, sex, current treatment for dyslipidemia or diabetes, and BMI were included as confounding variables (BMI was not used for Weight Excess analysis, treatment for diabetes was not used for hyperglycemia assessment, and treatment for dyslipidemia was not used for high serum triglyceride analysis). An admixture-adjustment was performed through a Monte-Carlo-Markov Chain where a three hybrid genetic stratification was assumed.

^aP values <0.025 were considered as statistically significant (Bonferroni correction).

^bAdmixture adjustment with Monte-Carlo-Markov Chain ($k=3$).

CI, confidence interval; OR, odds ratio.

Statistically significant values are highlighted in *bold*.

first evidence of that relationship found in a Latin American population. In contrast, the SNP *rs926198* showed no significant relationships, which represent a result that differs from previous findings on this particular issue.

To date, there is little evidence describing an association between *CAVI* and the metabolic syndrome itself. The most representative findings were published by Baudrand et al. who analyzed the *rs926198* *CAVI* SNP and found a significant association (OR=2.83, $p<0.001$) in a cohort with European ancestry and also replicated this finding in a second cohort of Hispanic subjects (OR=1.61, $p=0.025$).¹⁹ In that study, the authors included two cohorts of subjects with hypertension, while the present work was developed on a cross-sectional design, which represents a major difference between both studies and might be a cause for the discrepancies. Since a longitudinal analysis of an ill group increases the discriminatory power for certain associations with small size effects, it is possible that our study was unable to detect increased risks attributed to *rs926198* among hypertensive groups. In contrast, it is plausible that positive findings with *rs11773845* might provide insight on the same association found by Baudrand et al.¹⁹

Regarding serum triglycerides, an association between *rs11773845* and hypertriglyceridemia has been found in the Latin American population by the present work, which supports the results from a preliminary study where a significant deviation in *CAVI* genotype distribution among subjects with elevated triglyceridemia was found.³¹ The results of the present work agree with *in vitro* assays,^{12–14,16}

but are not in agreement with most human studies. To this point, it is important to note that none of the previous genetic association studies assessed the same *rs11773845* SNP, and although Pojoga et al. used this locus to analyze associations with insulin resistance and hypertension, they did not analyze high serum triglycerides.²⁰ There are previous studies where the genetic association between *CAVI* and serum triglycerides has been assessed.^{23,62} However, those studies were focused on two different *CAVI* SNPs, not on *rs11773845*. Moreover, those previous works have approached the serum triglyceride levels as a continuous variable instead of a categorical condition, which seriously modifies the results and interpretation of the analytical procedures and might be a cause of the discrepancies between and within association studies.⁶³ It is remarkable that in our study the null-hypothesis test showed no statistically significant results when triglyceridemia was analyzed as a continuous treat, but in a generalized linear model applied to data from the current work (with age, sex, and BMI as covariates) a marginal genetic association was found ($p=0.04$). These findings suggest a tenuous relationship that might be closely analyzed in further studies.

It has been shown by other authors that statin treatment for dyslipidemia is associated with body weight augmentation and changes in body fat distribution.⁶⁴ In addition, these drugs have been related to a higher incidence of diabetes.⁶⁵ In the same way, some antihypertensive drugs (*e.g.*, beta-blockers) have been related with weight gain,^{66,67} while metformin treatment against diabetes is associated with

TABLE 6. ASSOCIATION ANALYSIS OF HAPLOTYPES DERIVED FROM GENOTYPED SINGLE NUCLEOTIDE POLYMORPHISM IN CAVEOLIN 1 GENE

Haplotype	<i>rs926198</i>	<i>rs11773845</i>	Frequency	High serum triglycerides			Metabolic syndrome		
				OR	95% CI	P	OR	95% CI	P
H1	T	C	18.9	0.56	0.40–0.78	0.004	0.59	0.42–0.82	0.006
H2	C	A	6.0	0.55	0.31–0.98	0.26	0.83	0.62–1.09	0.574
H3	C	C	24.5	0.85	0.64–1.12	0.80	0.74	0.42–1.29	0.836
H4	T	A	50.6	1	NA	0.003	1	NA	0.007

weight loss, and an insulin-based treatment usually increases body weight.^{68,69} Under these considerations, a clinical record of ongoing treatment for dyslipidemia, hypertension, or diabetes was considered as a potential confounding variable and was included in the fitted additive models. Despite suspicions, statistically significant genetic associations with hypertriglyceridemia and metabolic syndrome were found, even when pharmacological treatment or diet was used as confounding variables. Similarly, these genetic associations persisted as a statistically significant result in a second analysis in which all subjects under treatment for metabolic disorders were excluded. This approach suggests that the relationships observed in this study might lie on alterations of metabolic pathways where caveolin 1 is involved (e.g., lipid droplet synthesis and insulin sensitivity, among others).⁷⁰ Although the influence of a single genetic variation on protein expression, cell function, and complex pathophysiological processes is thought to be unlikely, the genotype/phenotype relation found in the present work could be highlighted to a group of genomic, epigenomic, and/or metabolic alterations with a sharper link to dyslipidemia and metabolic disorders. In this sense, the role of *CAVI* variations in signalosomes and cellular pathways where caveolae/caveolin 1 is included might be an interesting focus for further studies.

In the present work nonconclusive associations between *CAVI* (rs11773845) and abdominal obesity were found in the logistic regression model and the MCMC; however, our results are suggestive of a hidden relationship. Since this anthropometric alteration is closely related with insulin resistance, this finding might note a previously known association between *CAVI* and insulin resistance. In our study, insulinemia was not a measured parameter; therefore, it was not possible to perform a direct assessment of this relationship. Naturally, the latter observation represents a limitation for this research since insulin resistance is highly involved in the development of metabolic and cardiovascular diseases, and it has been also associated with variations in *CAVI* by other authors.^{19,20}

Serum glucose and hyperglycemia were not associated with genetic variations in *CAVI*. This finding agrees with previous studies where glycemia and high serum glucose were not related with SNPs in *CAVI*. Although caveolin 1 and caveolae have been found to be involved in carbohydrate metabolism,^{8–11} it is plausible that rapid homeostatic regulation might compensate the effects of genetic variations on serum glucose concentrations. On this topic, there is evidence in which *CAVI* polymorphisms are linked with insulin resistance and diabetes,^{19,22} and both alterations are related with glucose homeostasis; however, there are not sufficient data in the present work to assess these genotype/phenotype relationships.

Regarding blood pressure, the results from our work have shown that there were differences in systolic and diastolic values when CC+TC and TT genotypes for rs926198 were compared ($p=0.02$), but there were no significant associations when the additive models were applied, even when subjects under antihypertensive treatment were excluded from regression analysis. In concordance with these results, the findings published by other authors are also controversial. For instance, several authors reported no significant results for genetic association in Chinese, Caucasian, and Hispanic populations, as well as other groups^{18,19,22,71};

however, Grilo et al. found a significant genetic association with exon variations in *CAVI*,¹⁸ and Pojoga et al. found evidence linking *CAVI* with hypertension in a translational study.²⁰ Since caveolae/caveolin 1 participate in artery relaxation, it is possible that positive results could be an insight into that role in the vasorelaxation pathway.⁷² Naturally, it seems that genetic variations in *CAVI* have a small size effect on blood pressure. Then negative results reflect a weak genotype/phenotype relationship.

Serum levels of HDL-C were found not associated with rs926198 or rs11773845, which agrees with results published by other authors. Chen et al. analyzed three independent samples accounting for a total of 6,185 subjects with Chinese Han ancestry and found no significant association between the SNP rs3807989 (*CAVI/CAV2* locus) and HDL-C levels.²³ Baudrand et al. found no association between rs926198 (*CAVI*) and low serum HDL-C in a study where a cohort with European ancestry and another with Hispanic background were analyzed.¹⁹ Peloso et al. analyzed *CAVI* (14 SNPs) in a set of 60 candidate genes involved in HDL-C metabolism and found 9 genes, but no SNP in *CAVI*, to be associated with susceptibility to dyslipidemia by low HDL-C.⁷³ On this basis, there is little evidence linking this gene with HDL-C alterations in human populations.

As it has been shown, there are several discrepancies between genetic association studies focused on *CAVI* and metabolic traits. This is an expected scenario considering that results from genetic association studies are not consistently reproducible.⁷⁴ Hence, interstudy comparisons are commonly an intricate task when a single or one-way relationship is a desirable finding.^{74,75} Such differences are caused not only by disease complexity but also by population diversity and heterogeneity in study designs.⁶⁰

Metabolic disorders and the metabolic syndrome are typical examples of complex diseases, where many gene-gene and gene-environmental interactions are taking place. About this issue, it has been proposed that discrepancies between studies, such as those exposed in the present work, might represent disease complexity and genetic diversity, instead of being a consequence of biased designs.^{55,74} In this regard, it has been proposed that discrepancies between studies, such as those exposed in the present work, might represent disease complexity and genetic diversity, instead of being a consequence of biased designs.^{60,75–78} Naturally, it is still possible that heterogeneity in the results could be caused by missing multiple interactions that are intrinsic to gene-candidate studies. To compensate these differences is not a feasible task in the current discussion. Perhaps, a meta-analytic approach would be able to summarize findings involving *CAVI* and metabolic traits.

Despite the statistical significance of the current findings involving high serum triglycerides and the metabolic syndrome, there are some limitations that should be considered. First, the study power is small; therefore some relevant interactions between genetic predictors and confounding variables could not have been detected. Under this consideration, adjustment for sex, age, BMI, and personal antecedents was carefully performed to reduce the significant affectations on the final results. Although analyses were carried out on a small sample size, it was possible to identify two genotype/phenotype associations even after a rigorous admixture adjustment with MCMC, which suggests that the current study design could have corrected most of the

concerning biases. Second, women showed higher frequencies for almost all metabolic alterations, which might be interpreted as a sign of selection bias; more importantly, half of the women were found to have metabolic syndrome, while it was diagnosed in 32.7% of men, suggesting that the affected women were more likely to be included in this sample. We have seen a similar behavior in previous works from Cartagena de Indias and Colombian Caribbean Coast³⁸; hence, statistical analysis was partially focused on fitting this problem. As supposed these results and our reasoning strongly encourage the development of a paired-sample case/control study aimed to bring conclusive evidence about the genetic association found in this population.

Interestingly, rs11773845 and rs926198 are in linkage disequilibrium with a third variation (rs3807989), which has been related to the expression of caveolin 1 mRNA in leukocytes, lymphoblastoid cells, and atrial tissue. In addition, some of these SNPs have been associated with serum caveolin 1 protein levels, which suggest a cellular and physiologic mechanism by which these intron variations would affect caveolin 1 gene expression with a subsequent impairment of lipid and carbohydrate metabolism.^{19,23,79} On this basis, we hypothesize that the complex caveolae/caveolin 1 might be a promissory target in the development of further therapies against high serum triglycerides and related metabolic disorders.

Conclusions

In conclusion, a statistically significant association between *CAVI* (rs11773845), high serum triglycerides, and metabolic syndrome was found in an admixed population from Latin America. This report supports preliminary findings that were suggestive of a relationship between *CAVI* and serum triglycerides in this population. Therefore, caveolae might be involved in lipid metabolism and related disorders in humans.

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Author Disclosure Statement

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