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ABOUT COVER

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WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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ORIGINAL ARTICLE

Retrospective Study

Differential distribution of gene polymorphisms associated with hypercholesterolemia, hypertriglyceridemia, and hypoalphalipoproteinemia among Native American and Mestizo Mexicans

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Abstract

BACKGROUND

Dyslipidemias are metabolic abnormalities associated with chronic diseases caused by genetic and environmental factors. The Mexican population displays regional differences according to ethnicity with an impact on the type of dyslipidemia.

AIM

To define the main dyslipidemias, the frequency of lipid-related risk alleles, and their association with hyperlipidemic states among different ethnic groups in West Mexico.

METHODS

In a retrospective study, 1324 adults were selected to compare dyslipidemias and lipid-related gene polymorphisms. Demographic, clinical, and laboratory data were collected. A subgroup of 196 normal weight subjects without impaired glucose was selected for the association analyses. Genotyping was determined by allelic discrimination assay.

RESULTS

Hypercholesterolemia was the most prevalent dyslipidemia (42.3%). The frequency of the risk alleles associated with hypoalphalipoproteinemia (*ABCA1*) and hypercholesterolemia (*APOE*, *LDLR*) was higher in the Native Americans (P = 0.047). In contrast, the Mestizos with European ancestry showed a higher frequency of the risk alleles for hypertriglyceridemia (*APOE2, MTTP*) (P = 0.045). In normal weight Mestizo subjects, the *APOB* TT and *LDLR* GG genotypes were associated risk factors for hypercholesterolemia (OR = 5.33, 95%CI: 1.537-18.502, P = 0.008 and OR = 3.90, 95%CI: 1.042-14.583, P = 0.043, respectively), and displayed an increase in low-density lipoprotein cholesterol levels (*APOB*: β = 40.39, 95%CI: 14.415-66.366, P = 0.004; *LDLR*: β = 20.77, 95%CI: 5.763-35.784, P = 0.007).

CONCLUSION

Gene polymorphisms and dyslipidemias showed a differential distribution. Regional primary health care strategies are required to mitigate their prevalence considering the genetic and environmental features which could have important implications for personalized medicine within the new era of precision medicine.

Key Words: Dyslipidemia; Ethnicity; Genes; Obesity; Lipids; Liver disease; Diet

Core Tip: Dyslipidemia is a metabolic alteration caused by gene-environmental interactions influenced by ethnicity. Genetic polymorphisms can modify the frequency and outcome of the hyperlipidemic state. Our results showed a differential distribution of gene polymorphisms associated with hypercholesterolemia (*APOE4*, *LDLR*), hypertriglyceridemia (*APOE2, MTTP*), and hypoalphalipoproteinemia (*ABCA1*) among Native Americans and Mestizo Mexicans of West Mexico. Hypercholesterolemia was the predominant dyslipidemia. In normal weight subjects, the *APOB* TT and *LDLR* GG genotypes increased the risk for hypercholesterolemia in the context of the Mestizo ethnicity. Regional personalized-medicine prevention strategies based on the host's genetic and environmental factors are required to decrease the prevalence of dyslipidemias.

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INTRODUCTION

Obesity is a leading health problem worldwide of epidemic proportions affecting the health of many societies regardless of socioeconomic status[1]. Currently, 75.2% of the Mexican adult population has excess weight (39.1% overweight and 36.1% obesity), and in recent years, Mexico has ranked first and second in the worldwide list of obesity[2,3]. Globalization is one of the main drivers of the national nutrition transition occurring in the last four decades[4]. It has shifted the consumption of the staple traditional Mexican diet towards high-calorie processed food products and sugary beverages, leading to unhealthy body weight and type 2 diabetes mellitus (T2DM) in the general population[5,6]. The leading causes of mortality in Mexico are T2DM, cardiovascular disease (CVD), and liver cirrhosis due to different etiologies; however, excess weight plays an important role in the development of these pathologies[7,8].

Dyslipidemia is one of the main metabolic alterations involved in these obesity-related co-morbidities [9]. Commonly, hypertriglyceridemia (HTG) is associated with insulin resistance which in turn causes both T2DM and liver fibrosis/cirrhosis, while hypercholesterolemia (HChol) is associated with CVD [10]. However, up to 30% of obese people do not have lipid abnormalities, while normal weight patients can present dyslipidemia[11,12]. It is also feasible that lean patients may present with nonalcoholic steatohepatitis (NASH), while some obese patients show no fatty liver or NASH[12]. These contrasting findings suggest that genetic and environmental factors are involved.

In terms of population genetics, 85% of Mexico's inhabitants are denoted Mestizos (MTZ) due to the admixture of Native American (NA), European, and African ancestral source populations that were

initiated 500 years ago after the Spanish conquest. In comparison, 10% and 5% are exclusively descendants of NA and African forefathers, respectively[13]. Concomitantly, with foodstuffs and food cuisine, a cultural syncretism between the eastern hemisphere (Spain, Africa, France, England) and the west (the Americas) took place, including the different geographic and ecological regions of Mexico[14]. Therefore, Mexico's population genetics and food culture are widely heterogenic, and the impact of these determinants can vary by region.

In this sense, the association of several single nucleotide polymorphisms (SNPs) located at different loci with dyslipidemias and their impact on non-communicable chronic diseases among the Mexicans has been acknowledged[15]. Distinctively, *APOE4*, *APOB* -516 C/T, as well as the *LDLR* A1413G and C52T are known to modulate the low-density lipoprotein cholesterol (LDL-c) levels and the susceptibility for HChol and CVD[16]. In the case of high-density lipoprotein cholesterol (HDL-c), the *ABCA1* R230C variant has been strongly associated with hypoalphalipoproteinemia (HALP), particularly in NA [17]. Additionally, the *MTTP*-943 G/T and the *MTHFR* C677T variants, as well as the *APOE2* allele, have been associated with increased triglycerides levels[18,19,20].

West Mexico´s population is characterized by NA inhabitants living in the rural areas, while the geographically dispersed MTZ populations have a variable degree of European and NA ancestries[21]. Previously, we documented that the *APOE4* allele is widespread among the NA but decreases significantly among the MTZ population with marked European ancestry, while conversely, the *APOE2* allele is predominant among this group[21,22]. However, studies jointly accessing these lipid-related gene polymorphisms have not been carried out among West Mexican populations. Thus, this study aimed to define the main dyslipidemias, the frequency of lipid-related risk alleles, and their association with hyperlipidemic states among different subpopulations.

MATERIALS AND METHODS

Study population and design

In this comparative cross-sectional study, a total of 1324 un-related adult individuals were retrospectively evaluated from January 2015 to December 2019 at the Department of Genomic Medicine in Hepatology, Civil Hospital of Guadalajara, "Fray Antonio Alcalde" in Guadalajara, Jalisco, Mexico. Each subject was interviewed, and a standardized questionnaire was used to register demographics, medical history, and laboratory data. The main exclusion criteria were the presence of any type of cancer, autoimmune and thyroid diseases, drug use in the last six months of recruitment, pregnant women, and use of hypolipidemic drugs.

In this study, populations of West Mexico with evidence of a representative NA ancestral component [22] were included, Nahua (NAH) (n = 84) and Wixárika (WXK) or "Huicholes" (n = 106) are indigenous ethnic groups, and five Mestizo populations: Guadalajara (GDL), Jalisco (n = 754), Tepic (TPC), Nayarit (n = 184), Cuquio (CUQ), Jalisco (n = 131), Villa Purificación (VP), Jalisco (n = 32), and San Miguel el Alto (SMA), Jalisco (n = 33). NA were identified according to the ethnic group, native language spoken, use of traditional attire, parents belonging to the ethnic group, and residence in a rural community. The Mestizo populations were defined as those born in Mexico, spoke Spanish, had Mexican parents, and did not belong to any native ethnicity.

For the association analyses between HChol and the related SNPs, 193 Mestizo subjects from GDL, Jalisco with normal weight determined by a body mass index (BMI) of 18.5-24.9 kg/m^2 and a body fat percentage of < 20% for men and < 30% for women, as well as without impaired glucose defined by fasting serum glucose of < 100 mg/dL and homoeostasis model assessment for insulin resistance (HOMA-IR) index < 2.5 were selected. This study subgroup was established as a reference population to decipher the influence of these genetic polymorphisms on dyslipidemia, since it is mestizo group with a more balanced genetic ancestry between NA and Europeans.

Definition for dyslipidemias

Dyslipidemias were defined according to the National Cholesterol Education Program expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (ATP III) and Mexican Official Norm 037 for the prevention, treatment, and control of dyslipidemias (NOM-037-SSA-2012): HChol was total cholesterol (TC) ≥ 200 mg/dL; HTG as triglycerides (TG) ≥ 150 mg/dL; HALP as HDL-c ≤ 40 mg/dL for men and ≤ 50 mg/dL for women; and high LDL-c as LDL-c ≥ 130 mg/dL[23,24].

Body composition

Body composition and BMI were assessed by bioelectrical impedance (InBody 3.0, Analyzer Body Composition, Biospace, South Korea) or a Tanita TBF_300A instrument (Tanita Corporation, Japan). Normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obesity (≥ 30 kg/m^2) were defined according to World Health Organization criteria[25].

Laboratory tests

Blood samples (10 mL) were obtained by venipuncture after a 12-h overnight fast. Biochemical tests included glucose, insulin, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, TC, TG, and HDL-c. All biochemical tests were determined with the AU5800 Clinical Chemistry System (Beckman Coulter's Inc. United States). The concentration of LDL-c was calculated using the Friedewald equation[26]. The very low-density lipoprotein-cholesterol (VLDL-c) was estimated by the formula of TC-(LDL-c + HDL-c). The HOMA-IR index was calculated with fasting plasma glucose (mg/dL) × fasting serum insulin (mU/L)/405. IR was defined as a HOMA-IR index of 2.5 or above to assess IR as a metabolic alteration.

DNA extraction and genotyping characterization

As previously described, genomic DNA (gDNA) was extracted from leukocytes using a modified salting-out method[27]. The genotypes of each SNPs were determined by a real-time PCR system using TaqMan® SNP Genotyping Assays (Applied Biosystems, Foster, CA, United States). The characteristics of context sequence of these probes correspond to the following catalog numbers: C_11720861_10 for *ABCA1* (rs9282541), C_7615488_10 for *APOB* (rs934197), C_8726910_10 and C_8726960_10 for *LDLR* (rs5930 & rs14158), C_1202883_20 for *MTHFR* (rs1801133), C_ 8934089_10 for *MTTP* (rs1800591), and C_3084793_20 and C_904973_10 for *APOE* (rs429358 & rs7412) (ThermoFisher Scientific). gDNA was used at a final concentration of 20 ng. PCR conditions were initial enzyme activation for 10 min at 95 °C, followed by 40 cycles of denaturalization for 15 s at 95 °C and alignment/extension for 1 min at 60 °C in a StepOnePlus thermocycler (Applied Biosystems, Foster, CA, United States). For genotype error checking, three positive controls corresponding to the possible genotypes for each SNP and a blank were included in every 96-well plate. A 20% of randomly selected samples were re-genotyped, of which 100% were concordant. Genotypic and allelic frequencies were obtained by the direct counting method. The Hardy-Weinberg equilibrium expectation was assessed by Arlequin version 3.1.

Statistical analysis

Kolmogorov-Smirnov test was used to analyze the normal distribution of all quantitative variables. Continuous variables were expressed as mean ± SD and categorical variables were reported as frequencies and percentages. Data with normal distribution was analyzed with parametric statistical tests (student's *t*-test and one-way ANOVA with the respective post-hoc analyses) and non-normal data through non-parametric statistical tests (Kruskal-Wallis and Mann-Whitney U). The chi-square was used when variables were categorical. Univariate and multivariate logistic and linear regression tests were performed to analyze the association of *APOB* -516C/T and *LDLR* A1413G SNPs as a risk factor for HChol. The results were expressed as odds ratio with 95%CI and R^2. All the tests with significant *P* value were corrected by the Bonferroni method. Statistical analyses were performed in the statistical program IBM SPSS Statistics version 21.0 for Windows (IBM Corp, Inc., Chicago, IL, United States). Statistical significance was set at $P < 0.05$ to two-tailed.

Ethical guidelines

The study protocol complied with the last updated ethical guidelines of the 2013 Declaration of Helsinki from Fortaleza, Brazil. This study was revised and approved by the Institutional Review Board. All patients signed a written informed consent before enrollment, and anonymized data was employed to continue the statistical analysis.

RESULTS

Clinical and lipidic characteristics of the study populations

The clinical characteristics and the lipid profile of study populations from West Mexico are depicted in Table 1. The average age and gender frequencies were similar among the seven groups, except for the higher frequency of men in the MTZ from TPC compared with the other groups ($P = 0.001$). All the groups had excess weight, but the MTZ group from GDL had the highest BMI (33.8 ± 10.3 kg/m^2, $P = 8 \times 10^{-27}$). The lipid profile showed differences by study group. MTZ from TPC had higher serum levels of TC, TG, and LDL-c compared to the rest of the study groups ($P < 0.05$). On the other hand, the NAH group showed lower levels of HDL-c than those from CUQ and WXK groups ($P = 0.011$).

Prevalence of dyslipidemias in West Mexico populations

Table 2 shows the prevalence of dyslipidemias in the populations from West Mexico. The most prevalent dyslipidemia was HChol, with 42.3%. HTG was detected in 40.4%, HALP in 37.8%, and high LDL-c in 35.8% of all study subjects. Among study populations, heterogeneity in the frequency of dyslipidemias was observed. The MTZ from TPC and VP had the highest frequency of HChol and HTG (75.5%, 65.6%, and 51.1%, 46.9% respectively, $P = 0.001$). The NAH group showed a lower frequency of HChol (7.1%), as well as MTZ from VP and WXK group a lower prevalence of HALP compared to the

Table 1 Clinical characteristics and lipid profile of West Mexico populations

Variables	Native American ancestry		Mestizos (low-to-high European ancestry)					Total WMX	*P* value
	NAH	WXK	TPC	GDL	CUQ	VP	SMA		
n (%)	84 (9.5)	106 (12.0)	184 (20.8)	321 (36.4)	131 (14.8)	32 (3.6)	26 (2.9)	884 (100)	
Age (yr)	29.5 ± 11	43.5 ± 15	52.5 ± 8.3	36.4 ± 12.6	48 ± 15.4	40.4 ± 21.1	44 ± 15	43.7 ± 14.8	0.022[a]
Male *n* (%)	24 (29)	41 (39)	77 (42)	91 (28)	34 (26)	13 (39)	9 (35)	289 (32.7)	0.001[d]
Female *n* (%)	60 (71)	65 (61)	107 (58)	230 (72)	97 (74)	19 (61)	17 (65)	595 (67.3)	0.001[d]
BMI (kg/m^2)	26.3 ± 4.3	ND	28.3 ± 4.7	33.8 ± 10.3	28.6 ± 5.8	26.4 ± 5.1	25.5 ± 3.8	29.9 ± 7.7	8×10^{-27}[c]
TC (mg/dL)	164.3 ± 39.8	190.4 ± 37.1	228.1 ± 49.2	187.7 ± 42.4	182.1 ± 34.4	210 ± 52.6	179.7 ± 37.2	199.3 ± 48.8	1×10^{-35}[a]
TG (mg/dL)	151.5 ± 86.2	150.6 ± 98.1	197.3 ± 123.6	161.6 ± 148.3	150.6 ± 95	171.7 ± 93.1	148.9 ± 86.4	169.7 ± 122.5	0.023[a]
LDL-c (mg/dL)	95.6 ± 30.3	120.2 ± 31.7	158.4 ± 46.4	114.5 ± 36.9	107.3 ± 9.1	141.5 ± 38.3	111.3 ± 30.3	128.8 ± 44.7	1×10^{-30}[a]
VLDL-c (mg/dL)	29.1 ± 28.6	24.8 ± 10.6	29 ± 16	32.6 ± 30.4	30.3 ± 19.2	36.2 ± 23.3	29.8 ± 17.3	30.4 ± 23.0	0.350
HDL-c (mg/dL)	39.5 ± 6.8	46.2 ± 10.6	41.1 ± 10.8	42.5 ± 14.4	44.0 ± 9.6	43 ± 3.5	39.9 ± 8.1	42.3 ± 11.2	0.010[b]

[a]Tepic (TPC) *vs* the other groups by post hoc tests, $P = 0.002$.
[b]Nahua (NAH) *vs* Cuquio (CUQ) & Wixárika group by post hoc tests, $P = 0.015$.
[c]Guadalajara (GDL) & NAH *vs* the other groups by post hoc tests, $P = 0.001$.
[d]TPC *vs* GDL, NAH & CUQ by post hoc tests, $P = 0.035$.
Values are presented as mean ± SD. Gender is expressed as number of cases and percentage. The one-way ANOVA for quantitative variables and Chi-square test for qualitative variables were the statistical approach. NAH: Nahua indigenous group; WXK: Wixárika indigenous group; ND: No data; TPC: Tepic; GDL: Guadalajara; CUQ: Cuquio; VP: Villa Purificación; SMA: San Miguel el Alto; WMX: West Mexico; BMI: Body mass index; TC: Total cholesterol; TG: Triglycerides; LDL-c: Low-density lipoprotein cholesterol; VLDL: Very low-density lipoprotein cholesterol; HDL-c: High-density lipoprotein cholesterol.

Table 2 Prevalence of the type of dyslipidemias in West Mexico populations

Dyslipidemia	Native American ancestry		Mestizos (low-to-high European ancestry)					Total WMX (*n* = 884)	*P* value
	NAH (*n* = 84)	WXK (*n* = 106)	TPC (*n* = 184)	GDL (*n* = 321)	CUQ (*n* = 131)	VP (*n* = 32)	SMA (*n* = 26)		
HChol	6 (7.1)	41 (38.7)	139 (75.5)	113 (35.2)	43 (32.8)	21 (65.6)	11 (42.3)	374 (42.3)	0.001[a]
HTG	35 (41.7)	36 (34.0)	94 (51.1)	116 (36.1)	49 (37.4)	15 (46.9)	12 (46.2)	357 (40.4)	0.001[b]
High LDL-c	13 (15.5)	43 (40.6)	137 (74.5)	72 (22.4)	24 (18.3)	21 (65.6)	7 (26.9)	317 (35.8)	0.003[a]
HALP	42 (50.0)	28 (26.4)	87 (47.3)	112 (34.9)	45 (34.3)	5 (15.6)	15 (57.7)	334 (37.8)	0.002[c]

[a]Tepic (TPC) *vs* the other groups.
[b]TPC *vs* Wixárika (WXK) & Cuquio (CUQ) group.
[c]Villa Purificación & WXK *vs* the other groups.
The Chi-square test was the statistical approach. Values are presented as number of cases and percentage. NAH: Nahua indigenous group; WXK: Wixárika indigenous group; TPC: Tepic; GDL: Guadalajara; CUQ: Cuquio; VP: Villa Purificación; SMA: San Miguel el Alto; WMX: West Mexico; HChol: Hypercholesterolemia; HTG: Hypertriglyceridemia; HALP: Hypoalphalipoproteinemia.

other study groups (15.6% and 26.4%, respectively, $P = 0.002$) (Table 2).

Frequency of risk alleles of SNPs associated with dyslipidemias in West Mexican populations

The genetic risk alleles associated with HALP (*ABCA1* R230C, RC + CC genotypes) and HChol (*APOE4* allele and *LDLR* 1413G allele) were more prevalent in the NAH and WXK groups compared to the other study groups ($P = 0.047$) (Table 3). The MTZ from VP and SMA showed a higher frequency of the risk alleles that have been associated with HTG (*APOE2* allele and *MTTP* -943G/T, T allele) compared with the other groups ($P = 0.045$) (Table 3).

Table 3 Frequency of risk allele of polymorphisms associated with lipid disorders in West Mexican populations

Lipid abnormality	SNPs (risk allele)	Native American ancestry		Mestizos (low-to-high European ancestry)					Total WMX (*n* = 1324)	*P* value
		NAH (*n* = 84)	WXK (*n* = 106)	TPC (*n* = 184)	GDL (*n* = 754)	CUQ (*n* = 131)	VP (*n* = 32)	SMA (*n* = 33)		
Low HDL-c	*ABCA1* R230C (RC + CC genotypes)	15 (17.9)	43 (40.6)	24 (13.0)	53 (7.0)	18 (13.7)	4 (12.5)	2 (6.1)	159 (12.0)	0.010[c]
High TC[e]	*APOE* (E4 allele)	21 (12.5)	53 (25.0)	ND	145 (9.6)	ND	2 (3.1)	2 (3.0)	223 (8.4)	2×10^{-12}[a]
	APOB-516C/T (T allele)	49 (29.2)	58 (27.4)	ND	433 (28.7)	ND	24 (37.5)	18 (27.3)	582 (22.0)	0.129
	LDLR A1413G (G allele)	121 (72.0)	161 (75.9)	ND	1045 (69.3)	ND	42 (65.6)	44 (66.7)	1413 (53.5)	0.047[a]
	LDLR C*52T (C allele)	124 (73.8)	145 (68.4)	ND	1068 (70.8)	ND	55 (85.9)	52 (78.8)	1444 (54.7)	0.045[b]
High TG[e]	*APOE* (E2 allele)	0 (0)	0 (0)	ND	51 (3.4)	ND	1 (1.6)	7 (10.6)	59 (2.2)	0.028[d]
	MTTP-493G/T (T allele)	17 (10.1)	2 (0.9)	ND	253 (16.8)	ND	11 (17.2)	10 (15.2)	293 (11.1)	2×10^{-6}[b]
	MTHFR C677T (T allele)	103 (61.3)	111 (52.4)	172 (46.7)	670 (44.4)	117 (44.6)	25 (39.1)	21 (31.8)	930 (35.2)	0.038[b]

[a]Nahua & Wixárika (WXK) *vs* the other groups.
[b]Villa Purificación & San Miguel el Alto (SMA) *vs* the other groups.
[c]WXK *vs* the other groups.
[d]SMA *vs* the other groups. The Chi-square test was the statistical approach.
[e]The allelic frequencies were obtained considering the diploid number of chromosomes (2n).
Values are expressed as *n* (%). NAH: Nahua indigenous group; WXK: Wixárika indigenous group; TPC: Tepic; GDL: Guadalajara; VP: Villa Purificación; SMA: San Miguel el Alto; WMX: West Mexico; ND: No data; HDL-c: High-density Lipoprotein cholesterol; TC: Total Cholesterol; TG: Triglycerides.

Association of APOB -516C/T and LDLR A1413G polymorphisms with hypercholesterolemia in normal-weight MTZ individuals

The clinical and biochemical characteristics of the 193 MTZ subjects selected to evaluate the possible effect of these Hchol-related polymorphisms are shown in Table 4. In this study subgroup, 38.9% (*n* = 75) had any type of dyslipidemia and HChol was the most prevalent with 27.9% (*n* = 54) (Table 4).

Table 5 depicts the lipid profile and frequency of dyslipidemias according to the SNPs *APOB* -516C/T and *LDLR* A1413G genotypes. *APOB* homozygous TT genotype carriers had significantly higher levels of TC (*P* = 0.033) and LDL-c (*P* = 0.017), as well as a higher frequency of HChol (*P* = 0.012) (Table 5). Besides, the carriers of the homozygous GG genotype of *LDLR* had significantly higher levels of LDL-c (*P* = 0.042) and higher frequency of HChol (*P* = 0.034) (Table 5).

As shown in Table 6, the frequency of subjects with HChol was greater among carriers of the homozygous genotypes TT of *APOB* and GG of *LDLR* than the non-HChol (26.1% *vs* 6.9%, *P* = 0.005; 60.9% *vs*. 38.6%, *P* = 0.043, respectively). Also, both genotypes, TT of *APOB* and GG of *LDLR* were associated with HChol (OR = 5.33, 95%CI: 1.537-18.502, *P* = 0.008; OR = 3.90 95%CI: 1.042-14.583, *P* = 0.043, respectively) (Table 6).

Finally, through a linear regression test, an increase of 30% higher LDL-c was associated with the homozygous TT genotype of *APOB* (R^2 = 0.30, β = 40.39, 95%CI: 14.415-66.366, *P* = 0.004), and an increase of 11% higher LDL-c was associated with the GG genotype of *LDLR* (R^2 = 0.11 β = 20.77, 95%CI: 5.763-35.784, *P* = 0.007) (Table 7).

DISCUSSION

Dyslipidemias are severe abnormalities commonly associated with excessive body fat, a pathogenic factor contributing to the development of co-morbidities such as T2DM, fatty liver disease, and CVD [28]. However, genetic and environmental factors cause differences across the country in the incidence of these pathologies. Previously, we have documented the admixed genetic architecture of West Mexico [21,22]. In this region, NAH and WXK are representative of the NA genetic component, while the inhabitants of TPC, GDL, CUQ, VP, and SMA are historically known to carry a significant European genetic component. Therefore, we hypothesized that the distribution of dyslipidemias and the lipid-related alleles could be variable according to the ancestral inheritance. Herein, we present the first study

Table 4 Clinical and biochemical characteristics and frequency of dyslipidemias in normal weight Mestizos individuals

Variable	Reference values	Study group
n		193
Age (yr)		32.8 ± 12.3
Male		55 (28.5%)
Female		138 (71.5%)
BMI (kg/m^2)	18.5-24.9	22.3 ± 1.1
Total body fat (%)	< 24%	21.3 ± 6.1
Glucose (mg/dL)	< 100	84.4 ± 7.9
HOMA-IR	< 2.5	1.7 ± 0.5
TC (mg/dL)	< 200	180.1 ± 33.1
TG (mg/dL)	< 150	112.2 ± 61.3
LDL-c (mg/dL)	< 130	109.2 ± 27.6
VLDL-c (mg/dL)	< 25	22.5 ± 12.3
HDL-c (mg/dL)	> 40	49.4 ± 13.7
AST (UI/L)	< 54	26.3 ± 10.5
ALT (UI/L)	< 42	25.1 ± 14.1
GGT (UI/L)	< 35	20.2 ± 5.3
Dyslipidemia		75 (38.9%)
HChol	(TC > 200 mg/dL)	54 (27.9%)
HTG	(TG > 150 mg/dL)	35 (18.1%)
High LDL-c	(LDL-c ≥ 130 mg/dL)	39 (20.2%)
HALP	(HDL-c < 40 mg/dL)	40 (20.7%)

Values are presented as mean ± SD; *n*: Number of cases and percentage. MTZ: Mestizo; BMI: Body mass index; HOMA-IR: Homeostasis model assessment insulin resistance; TC: Total cholesterol; TG: Triglycerides; LDL-c: Low-density lipoprotein cholesterol; VLDL-c: Very low-density lipoprotein cholesterol; HDL: High-density lipoprotein cholesterol; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl-transferase; HChol: Hypercholesterolemia; HTG: Hypertriglyceridemia; HALP: Hypoalphalipoproteinemia.

jointly detecting several lipid-related risk alleles that confer dyslipidemia among the West Mexican population. An evident heterogeneity in the type of dyslipidemia and lipid-related risk alleles was observed between the study groups consistent with their genetic and environmental background.

Overall, the most prevalent dyslipidemia was HChol (42.3%). These data were discrepant with the National Health and Nutrition Survey 2006 and 2018, with HALP in nearly 60% nationwide[29,30]. A plausible explanation is that national surveys tend to focus on central regions of the country in which the NA component is predominant compared to West Mexico, in which the European ancestry is more prevalent. Furthermore, the breakdown analysis of the type of dyslipidemias adjusted by study group revealed that the NA had lower HChol (7.1%) while the MTZ from TPC and VP had higher rates of HChol (75.5% and 65.6%) and HTG (51.1% and 46.9%), respectively.

Given this panorama of dyslipidemias, we explored the frequency of several SNPs associated with these lipid abnormalities finding that the NA groups showed genetic susceptibility for HChol and HALP (*ABCA1* 230C allele, *APOE4* allele and *LDLR* 1413G allele); while the frequency of the risk alleles associated with HTG (*APOE2* allele and *MTTP* -943T allele) were higher in MTZ groups with a significant European ancestry. Notably, the *MTHFR* 677T risk allele prevalence revealed a high to low gradient (from NA to MTZ) which may have implications for fatty liver disease[31]. Thus, in conjunction, these findings highlight the importance of considering the ancestral components regarding the genetic susceptibility for lipid-related chronic diseases.

Furthermore, in this study, the TT genotype of *APOB* and GG genotype of *LDLR* were associated as risk factors for HChol. APOB is the main structural protein of LDL lipoprotein, essential for the assembly and secretion of chylomicrons and VLDL lipoprotein, and it is the primary ligand for LDLr mediated internalization of LDL-c in target tissues[33]. An imbalance between the production and degradation of APOB-containing lipoproteins leads to the development of HChol and, potentially, atherosclerosis[32]. In this context, *in vitro* studies have documented that the "T" allele of the *APOB*

Table 5 Association of *APOB* -516C/T and *LDLR* A1413G polymorphism with lipid levels in normal weight Mestizos individuals

Variable	*APOB* -516 C/T genotypes			*P* value	*LDLR* A1413G genotypes			*P* value
	CC (*n* = 85)	CT (*n* = 54)	TT (*n* = 15)		AA (*n* = 22)	AG (*n* = 65)	GG (*n* = 63)	
TC (mg/dL)	177.8 ± 31	178.2 ± 37.4	196.2 ± 27.6	0.033[a]	177.2 ± 25.7	175.4 ± 33.1	182.9 ± 34.7	0.366
TG (mg/dL)	110.4 ± 68	119.9 ± 71.3	108.7 ± 25.9	0.574	106.9 ± 47.5	98.7 ± 44.6	124.3 ± 79.8	0.094
LDL-c (mg/dL)	106.3 ± 24	107.3 ± 30.6	129.5 ± 31.6	0.017[a]	103.3 ± 23.9	106.2 ± 26.8	111.8 ± 29.5	0.042[b]
VLDL-c (mg/dL)	22 ± 13.6	24.3 ± 14.3	21.8 ± 5.1	0.451	21.3 ± 9.5	19.7 ± 9.0	25.1 ± 16.0	0.075
HDL-c (mg/dL)	49.3 ± 13.9	48.5 ± 10.7	50.3 ± 16.9	0.908	51.1 ± 15.3	51.6 ± 11.8	46.8 ± 13.3	0.143
Dyslipidemia, *n* (%)								
HChol	9 (11)	8 (15)	6 (40)	0.012[a]	1 (5)	8 (12)	14 (22)	0.034[b]
HTG	15 (18)	14 (26)	0 (0)	0.076	3 (14)	7 (11)	15 (24)	0.315
High LDL-c	13 (15)	12 (22)	7 (47)	0.007[a]	3 (14)	10 (15)	17 (27)	0.046[b]
HALP	19 (22)	10 (18)	3 (20)	0.760	3 (14)	8 (12)	18 (13)	0.178

[a]TT *vs* CC.
[b]GG *vs* AA.
The Kruskall Wallis test and U Mann-Whitney test for quantitative variables and Chi-square test for qualitative variables were the statistical approach. Values are expressed as mean ± SD, number of cases and percentage. MTZ: Mestizos; TC: Total cholesterol; TG: Triglycerides; LDL-c: Low-density lipoprotein cholesterol; VLDL-c: Very low-density lipoprotein cholesterol; HDL-c: High-density lipoprotein cholesterol; HChol: Hypercholesterolemia; HTG: Hypertriglyceridemia; HALP: Hypoalphalipoproteinemia.

Table 6 Association of *APOB* and *LDLR* genotypes with hypercholesterolemia in normal weight Mestizos individuals

Genotype	Non-HChol	HChol	*P* value	Genotype comparison	Odds ratio (95%CI)	*P* value
APOB -516C/T genotypes						
CC	76 (58.0%)	9 (39.1%)	0.120	TT *vs* CC	5.33 (1.537-18.502)	0.008
CT	46 (35.1%)	8 (34.8%)	0.895	TT *vs* CC + CT	4.63 (1.463-14.634)	0.009
TT	9 (6.9%)	6 (26.1%)	0.005	TT *vs* CT	3.83 (1.069-13.746)	0.039
LDLR A1413G genotypes						
AA	21 (16.5%)	1 (4.3%)	0.135	GG *vs* AA	3.90 (1.042-14.583)	0.043
AG	57 (44.9%)	8 (34.8%)	0.340	GG *vs* AA + AG	2.53 (1.216-5.282)	0.013
GG	49 (38.6%)	14 (60.9%)	0.043	GG *vs* AG	2.24 (1.028-4.890)	0.042

Values are expressed as number of cases and percentage. MTZ: Mestizos; HChol: Hypercholesterolemia. The Chi-square test and logistic regression test were the statistical approach.

-516C/T polymorphism increases the transcription of the *APOB* gene by more than 40%. Consequently, this causes a substantial increase in plasma LDL-c concentration[34].

Moreover, it was reported that in a healthy Swedish population, the -516T allele of this SNP increased the plasma LDL-c concentration by 12%, and in a French population was associated with a high plasma LDL-c concentration and the presence of carotid atherosclerotic disease[34,35]. In this study, the TT genotype of *APOB* -516C/T polymorphism increased the plasma LDL-c concentration by 30% in lean subjects. This is the highest percentage of LDL-c increase associated with the TT genotype of *APOB* reported so far. This information highlights that despite a lower frequency of -516T allele of *APOB* compared to other populations, the genetic effect on the plasma LDL-c concentration is more remarkable.

The most common genetic causes of HChol are mutations in the gene that codes the LDLr. These mutations drastically alter the functional activity of this surface receptor, thereby delaying the clearance of LDL particles[36]. Several studies have documented the relation of *LDLR* A1413G polymorphism with pathologies involving lipid disorders. For example, this genetic variant was found in 17% of patients with familial hypercholesterolemia from Iran[37], and in the United States, this same polymorphism was associated with Alzheimer's disease[38]. In this study, the GG genotype of *LDLR*

Table 7 Increased serum level of low-density lipoprotein cholesterol associated with *APOB* and *LDLR* genotypes in individuals with normal weight from West Mexico

Genotype comparison	R^2	β	95%CI	*P* value
APOB -516C/T				
TT *vs* CC	0.30	40.39	14.415-66.366	0.004
TT *vs* CC + CT	0.23	39.79	16.226-63.363	0.001
TT *vs* CT	0.31	39.01	0.996-67.029	0.091
LDLR A1413G				
GG *vs* AA	0.11	23.29	1.640-44.946	0.036
GG *vs* AA + AG	0.11	20.77	5.763-35.784	0.007
GG *vs* AG	0.08	19.74	0.915-37.270	0.082

Linear regression test was the statistical approach.

A1413G polymorphism was associated with HChol and increased plasma LDL-c concentration by 11%. This study is the first to establish a direct association between the GG genotype of *LDLR* with the levels of LDL-c and the presence of hypercholesterolemia in a healthy population from Mexico and Latin America.

The implications of these findings require addressing the role of the interrelationship between diet-related adaptive alleles and the current diet of the population. In this sense, NA groups have followed a frugal lifestyle for millennia in which lipid-related alleles may have been positively selected to cope with the Paleolithic and Neolithic Mesoamerican environments[39]. Their traditional diets mainly contained low amounts of saturated fats and were high in mono- and polyunsaturated vegetal fats and high complex carbohydrates which are protective against lipid-related chronic diseases despite the host's "risk alleles"[40,41]. However, lifestyle changes caused by the current nutrition transition place at risk both the NA population and MTZ, regardless of the degree of European ancestry. Likewise, the MTZ may be at higher risk for HTG particularity if they are carriers of the European risk alleles if changes in the dietary pattern occur. In this sense, the current dietary patterns in Mexico are notably unhealthy, characterized as obesogenic and hepatopathogenic leading to considerable increase in the prevalence of non-communicable chronic diseases such as T2DM, CVD, and nonalcoholic fatty liver disease[12,20,41,42].

Furthermore, dietary patterns are different by region nationwide. In West Mexico, the intake of pork meat is higher throughout the entire year. A traditional practice is eating pork rind "carnitas," cracklings, and doing barbecues almost every weekend. On the other hand, the fast-paced lifestyle in the central region of the country led to the consumption of processed food, which is rich in saturated fatty acids, trans fat, and simple carbohydrates[42]. These elements have been associated with the presence of dyslipidemias, particularly HTG and HALP[43]. These results reflect that the epidemiological pattern of dyslipidemias is not homogeneous throughout the country and the necessity to perform comparatively specific studies per region in Mexico and other countries.

This study has some limitations. First, despite that several representative populations of West Mexico with different ancestral compositions were included, it was not possible to complete the genetic profile of all populations. Nonetheless, the frequencies of risk alleles reported in this study are sufficient to demonstrate a differential distribution of gene polymorphisms associated with dyslipidemias among Native Americans and Mestizo Mexicans (Table 3). Next, the cross-sectional design may limit a complete extrapolation of the results obtained. Finally, the data was recorded through standardized questionnaires that provide sufficient and detailed information; information bias may be present. Thus, further prospective and longitudinal studies involving lipid-related genetic variants and lifestyle factors (physical activity, behavior, and mental health) are required.

In summary, the frequency of dyslipidemias in West Mexico differed from the national reports. The NA groups (WXK and NAH) showed a greater genetic susceptibility for developing HChol and HALP. The TT genotype of *APOB* -516C/T and GG genotype of *LDLR* A1413G were associated as risk factors for HChol and increased LDL-c levels in Mestizo healthy population.

CONCLUSION

Given the differential distribution of gene polymorphisms and rate of dyslipidemias found in this study, primary health care strategies are required to establish preventive actions to mitigate their prevalence

considering the regional genetic and cultural differences, which could have important implications for personalized medicine within the new era of precision medicine.

ARTICLE HIGHLIGHTS

Research background

Further investigations are needed to provide medical and nutritional therapies based on the genetic background of the population and the role of lifestyle changes including diet, exercise and mental health.

Research motivation

Given the differential distribution of gene polymorphisms and rate of dyslipidemias found in this study, primary health care strategies are required to establish preventive actions to mitigate their prevalence considering the regional genetic and cultural differences, which could have important implications for personalized medicine within the new era of precision medicine.

Research objectives

We aimed to describe if there are important differences between Native American and Mestizo Mexicans in regard to the type of dyslipidemias and lipid-related genetic polymorphisms.

Research methods

In this retrospective study, 1324 adults were selected to compare dyslipidemias and lipid-related gene polymorphisms. Demographic, clinical, and laboratory data were collected. A subgroup of 196 normal weight Mestizo subjects without impaired glucose was selected for the association analyses. Genotyping was determined by allelic discrimination assay.

Research results

The Native Americans showed a greater genetic susceptibility for developing hypercholesterolemia (HChol) (*APOE4*, *LDLR*) and hypoalphalipoproteinemia (*ABCA1*). The TT genotype of *APOB* -516C/T and GG genotype of *LDLR* A1413G were associated risk factors for HChol and increased low-density lipoprotein cholesterol levels in Mestizo healthy population.

Research conclusions

Deciphering the role of ethnicity in the type of dyslipidemia and defining the prevalence of lipid-related gene polymorphisms.

Research perspectives

Genetic and environmental factors are involved in the onset and progression of dyslipidemias among the Mexican population.

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FOOTNOTES

Author contributions: Panduro A conceived and designed the study; Torres-Valadez R, Ojeda-Granados C and Gonzalez-Aldaco K carried out experimentation, and data collection; Panduro A, Torres-Valadez R, Roman S, Ojeda-Granados C, Gonzalez-Aldaco K did analyses and interpretation of data; Torres-Valadez R drafted the manuscript. All authors critically revised the manuscript for intellectual content. All authors revised and approved the final version of the manuscript.

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Informed consent statement: All patients signed a written informed consent before enrollment, and anonymized data was employed to continue the statistical analysis.

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