Obesity Research & Clinical Practice 13 (2019) 533–540

Contents lists available at ScienceDirect

Obesity Research & Clinical Practice

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

Original Article

Contribution of genetic, biochemical and environmental factors on insulin resistance and obesity in Mexican young adults

Karla Lucero Flores-Viveros[a], Beatriz Adriana Aguilar-Galarza[a], María Luisa Ordóñez-Sánchez[b], Miriam Aracely Anaya-Loyola[a], Ulisses Moreno-Celis[a], Paola Vázquez-Cárdenas[c,*], Teresa García-Gasca[a,*]

[a] Facultad de Ciencias Naturales, Universidad Autónoma de Querétaro, Av. de las Ciencias S/N, Juriquilla, Querétaro, CP, 76230, Mexico
[b] Unidad de Biología Molecular y Medicina Genómica, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
[c] Centro de Innovación Médica Aplicada, Clínica de Obesidad, Hospital General Dr. Manuel Gea González, 14080, CP, Mexico City, Mexico

ARTICLE INFO

Article history:
Received 31 March 2019
Received in revised form
29 September 2019
Accepted 31 October 2019

Keywords:
Young adults
Obesity
Insulin resistance
Metabolic syndrome
Genetic variants

ABSTRACT

Overweight/obesity, dyslipidemias, hypertension and hyperglycemia are strongly related to non-communicable diseases (NCD) in which genetic and environmental factors interact with each other. The Mexican population exhibit a genetic disposition to metabolic syndrome, type 2 diabetes, as well as many forms of dyslipidemia. This study aimed to determine the association between biochemical, genetic and environmental factors in the development of metabolic syndrome (MS), obesity and insulin resistance (IR) in Mexican young adults. Young women and men (n = 6750 between 19.3 ± 2.3 years old) participated in a health promotion program from the Autonomous University of Querétaro, México (*SU-Salud* program). A sub-sample of 665 participants was taken for the determination of single nucleotide polymorphisms (SNP) rs964184 (APOAV), rs9282541 (ABCA1) and rs1260326 (GCKR), using QuantStudio 12 K Flex Real-Time PCR System. For the multivariate analysis, a multiple logistic regression was performed. A prevalence of 22% of overweight and 7% of obesity was determined. The main metabolic risk factors were low levels of HDL-C (30%), IR (19%), and a high level of triglycerides (15%). The main factors associated with IR were body fat percentage and triglycerides; SNP for the ABCA1 gene was related to MS, obesity and low HDL-C; SNP for GCKR gene was related to high fasting glycemia, while APOAV SNP was related with MS, hypertriglyceridemia and low HDL-C. Our findings show that the Mexican genetic predisposition to NCD affects young adults, who can suffer MS, obesity and IR. Public health strategies must focus on prevention actions from an early age.

Introduction

According to the World HealthOrganization (WHO), high blood pressure (HBP), overweight/obesity, dyslipidemias and hyperglycemia are metabolic alterations related to non-communicable diseases (NCD) [1], which are the leading cause of premature death in the world. More than 36 million people die each year from NCD; of these, nine million are premature deaths since they occur in people under 60 and are the cause of 58% of the years lost because of premature death in Mexico [2]. The evolution of NCD is largely due to genetic factors [3], environmental factors, such as the consumption of tobacco and/or alcohol, physical inactivity, and an inadequate diet. Such risk factors provoke metabolic alterations, including metabolic syndrome (MS), insulin resistance (IR) obesity, lipotoxicity and dyslipidemias [4]. IR is defined as the decrease in the ability of insulin to exert its biological actions on target tissues such as skeletal muscle, liver or adipose tissue [5]. Chronic IR is an etiological factor of various metabolic diseases such as type 2 diabetes mellitus (DM2) [6]. Since 2007, with the Genome-wide association study (GWAS), importance has been given to the identification of common genetic variants that contribute to the risk of complex diseases in different populations [7]. It is known that about 50% of the variability of obesity and IR is genetically determined [8]. It has been shown that the Mexican population has a genetic predisposition to metabolic syndrome, DM2, as well as dyslipidemias. To date, 95 loci associated with plasma lipid concentrations have been identified, 24 of which are involved with triglyceride con-

* Corresponding authors.
E-mail addresses: paola.vazquez@icloud.com (P. Vázquez-Cárdenas), tggasca@uaq.edu.mx (T. García-Gasca).

https://doi.org/10.1016/j.orcp.2019.10.012
1871-403X/

centrations and 38 with HDL concentrations [9]. The risk genotype is associated with a low response to treatment and with a high risk of type 2 diabetes mellitus, hyperlipidemias and cardiovascular complications.

Youth is characterized as a favorable period in terms of the health status of the population, so it has been little studied. However, this sector of the population is at risk, as neither age nor phenotype guarantee the absence of subclinical metabolic alterations that may trigger NCD. Given that NCD occur as a result of a long process of evolution, it is essential to study subclinical and early clinical risk factors in the young population in order to identify the main alterations that promote NCD decades later. Therefore, the present work aimed to determine the association between biochemical, genetic and environmental factors with overweight/obesity, MS and IR susceptibility in Mexican young adults.

Materials and methods

Participants

In this study, 6750 participants (aged between 17 and 23 years) from the Autonomous University of Querétaro (México), who were participating in the health promotion program *SU-Salud* from 2012 to 2017 were included. Since blood samples for DNA isolation were available only for 665 of the participants enrolled in the program in 2017, this sub-sample was used for the genetic variant analysis. This study was approved by the Bioethics Committee of the Natural Sciences Faculty of the Autonomous University of Querétaro under the guidelines of the Declaration of Helsinki [10]. All participants signed an informed consent form before starting.

Clinical history and questionnaires

Clinical history was obtained by an interview to collect general, personal and family data. Blood pressure and vital signs were obtained by a physician. Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) [11]. Self-applicable questionnaires of lifestyle habits with open and closed questions on lifestyle habits were applied to assess environmental risk factors such as consumption of breakfast, alcohol consumption and smoking. The presence of environmental risk factors was defined according the following criteria: sedentary when young people practiced less than 150 min of physical activity on a week; consumed soda at least once a day; consumed alcohol, drank at least one alcoholic beverage a week; skipped breakfast or those that were not used to having breakfast any day of the week. Food insecurity was also assessed by the ELCSA questionnaire [12].

Nutritional study

Anthropometric measures (height, waist circumference and hip circumference) were done in duplicate. Waist circumference was measured at the midpoint between the iliac crest and the last rib, and hip circumference was measured sideways at the maximum circumference around the buttocks. Body Mass Index (BMI) was calculated as body weight (in kg) divided by the square of body height (in m), waist to hip ratio (WHR) was calculated by dividing waist circumference by hip circumference (in cm), and waist to height index (WHI) was calculated by dividing height (in m) and waist (in cm). Body weight and body composition were assessed through bioimpedance analysis using a SECA 514 medical body composition analyzer (mBCA; Seca Deutschland, Hamburg, Germany). The mBCA device has a standing platform with an integrated scale and a handrail system, with one pair of electrodes for each hand and foot (eight-electrode). Fat mass (FM) and fat-free mass (FFM) were derived from predictive equations that had been validated against reference methods [13].

Blood sample

A blood sample was taken after a fast of 12 ± 2 h by venipuncture in the arm, using 5-mL serum separation tubes for serum collection (Vacutainer-Becton-Dickinson) and 4-mL EDTA tubes (Vacutainer-Becton-Dickinson) for total blood and plasma collection. The blood sample was centrifuged at 2500 rpm for 10 min to obtain serum or plasma.

Biochemical markers

Glucose, total cholesterol, triglycerides and HDL-C were determined using the serum via a colorimetric enzymatic technique using an automated Mindray equipment BS 120. The quantification of insulin was determined from plasma by using an ELISA 80-INSHU-E01.1 kit (ALPCO, Windham, NH, USA). The HOMA index was calculated according to the mathematical equation HOMA-IR = Insulin (μU)/L) x Glucose (mmol/L)/22.5, proposed by Matthews et al [14]. The cutoff values were used according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents [15]. Values for insulin and HOMA index were considered according to those suggested by Murguía-Romero et al. for the young Mexican population [16].

Classification of metabolic syndrome was according to the International Diabetes Federation (IDF) [17], defined as three of the following five factors: triglycerides ≥150 mg/dL, high-density lipoprotein (HDL) <40 mg/dL for males and <50 mg/dL for females, glucose ≥110 mg/dL, waist circumference >80 cm for females and >90 cm for males and hypertension (systolic BP > 129 and diastolic BP > 85 mmHg).

Genetic assays

DNA was isolated from whole blood (200 μL) using a QIAamp 96 DNA blood kit (QIAGEN, Valencia, CA) according to the manufacturer's protocol and recommendations. The concentration and 260/280 quality ratio for all the isolated DNA samples were determined using the Nanodrop spectrophotometer (Wilmington, DE) and stored at −20 °C until use. Genomic DNA was diluted to a final stock concentration of 25 ng/mL using DNAase-free water. All DNA samples had a purity of 1.8–2.0. Genotyping was performed using QuantStudio 12 K Flex Real-Time PCR System by the *Red de Apoyo a la Investigación* (RAI) at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Custom Open Array Chips (Thermo Fisher Scientific, Waltham, MA, USA) were designed with selected polymorphisms of interest (rs964184 [APOAV], rs9282541 [ABCA1] and rs1260326 [GCKR]), which have been observed to be related to plasma lipid levels and cardiovascular risk. The chip was created based on polymorphism ID from NCBI polymorphism database and assay ID of the catalog C_8907629_10 for APOAV, C_11720861_10 for ABCA1 and C_2862880_1_ for GCKR. All the genetic variants were found in Hardy Weinberg equilibrium ($p > 0.05$), and genotyping call rates were above 99%, with a re-genotyping concordance rate >99%.

Statistic analyses

Means ± standard deviations for continuous variables and percentages for categorical variables were determined. The normality of the variables was tested (Kolmogorov–Smirnov test with Lilliefors correction). Student's T-tests were performed for continuous variables and chi square (X^2) for the categorical ones. Logistic

Table 1
General characteristics of the total sample.

	Men	n = 3571		Women	n = 3179		Total	n = 6750		*p* value
Age, y	19.3	±	1.8	19.1	±	1.6	19.3	±	2.3	0.001
Weight, kg	70.9	±	14.3	58.4	±	10.6	65.1	±	14.2	0.001
Height, cm	172.3	±	6.4	159.5	±	5.8	166.3	±	8.9	0.001
BMI, kg/m^2	23.8	±	4.3	22.9	±	3.8	23.4	±	4.2	0.001
Waist, cm	82.1	±	11.1	74.7	±	9.2	78.6	±	11.0	0.001
Hip, cm	96.7	±	8.5	95.8	±	7.9	96.3	±	8.3	0.001
WHR	0.84	±	0.05	0.77	±	0.05	0.81	±	0.06	0.001
WHI	0.48	±	0.74	0.46	±	0.05	0.47	±	0.52	0.104
Total body fat, %	20.8	±	7.6	30.1	±	6.6	25.2	±	8.4	0.001
Glucose, mg/dL	85.6	±	11.7	82.3	±	11.1	84.2	±	12.6	0.001
Triglycerides, mg/dL	113.8	±	67.0	94.2	±	49.2	105.2	±	61.2	0.001
Cholesterol, mg/dL	158.5	±	33.1	158.8	±	31.0	158.8	±	31.9	0.641
HDL-C, mg/dL	48.6	±	11.1	55.1	±	13.6	51.6	±	12.8	0.001
LDL-C, mg/dL	87.8	±	24.0	86.8	±	22.5	87.3	±	23.3	0.107
Insulin, μg/mL	8.8	±	7.7	9.1	±	7.1	9.0	±	7.4	0.233
HOMA-IR	1.9	±	1.7	1.9	±	1.5	1.9	±	1.6	0.891

BMI, body mass index; WHR, waist to hip ratio; WHI, waist to height index; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance. Values are shown as the mean ± SD. *P* value ($p \leq 0.05$) of Student́s test for the difference of means between and women.

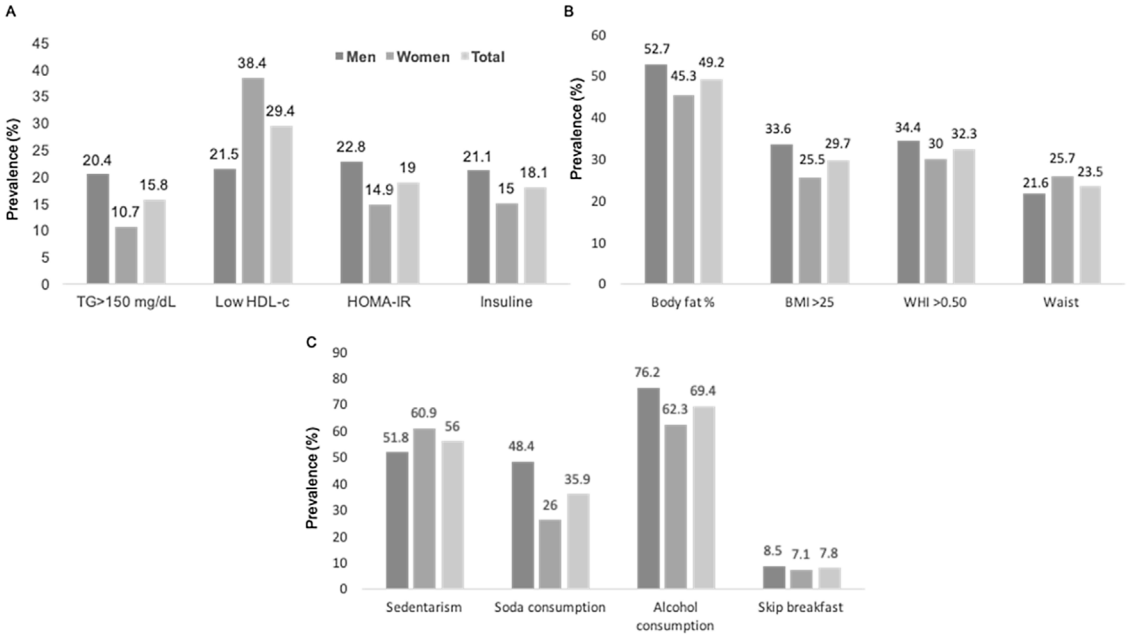

Fig. 1. Prevalence of biochemical alteration and frequency of environmental risk factors.
(A) Biochemical factors, TG; triglycerides; Low HDL-C <50 mg/dL in female and <40 mg/dL in male; HOMA-IR >2.9 in female and >2.3 in male; insulin >14 μU/ml in female and 11 μU/ml in male. (B) Anthropometric factors, body fat >30% in female and >20% in male; waist >80 cm female and >90 cm in male. (C) Lifestyle habits.

regression was performed for the analysis of categorical traits to determine the association of metabolic risk and exposure to the biochemical and genetic factors analyzed. Logistic regression was used to assess the association of the genotypes (minor allele non-carrier and minor allele carrier) with insulin resistance and lipid phenotypic variations in interaction with BMI >25% body fat, sedentarism and sugar intake, adjusted for age and sex. Statistical analyses were performed using the SPSS Version 22.1 package (IBM Software Group A, Chicago, IL, USA).

Results

Prevalence of risk factors and metabolic alterations

A total of 6750 subjects participated in this study, 53% of which were men and 47% women, with and an average age of 19.3 ± 2.3 years. The general characteristics of the studied population are shown in Table 1. Significant differences between the anthropometric variables were observed by sex. Based on the BMI, the general prevalence of overweight (OW) was 22% and 7% for obesity (OB). Men showed a higher prevalence for OW and OB (25% and 9%, respectively), than females (19% and 6%, respectively) (Fig. 1). Moreover, 49.2% showed an elevated proportion of body fat in men (53% vs 45% in women). The mean values of glucose and triglyceride concentrations were significantly higher in males than in females ($p \leq 0.05$).

Fig. 1 shows the prevalence of alteration for biochemical and frequency of environmental risk factors. HDL-C presented lower average serum concentrations in men than in women, however, 38% of females presented low HDL-C (<50 mg/dL). The prevalence of metabolic syndrome was of 5.45% (5.4% in females and 5.5% in males). The most prevalent biochemical risk factors found were low HDL-C (30%), insulin resistance (IR) (19%) and high triglycerides (HTG) (15.8%). Between the analyzed environmental factors, 7.8% skip breakfast, 35.9% of the participants reported daily soda con-

Table 2
Association between BMI and insulin resistance with biochemical and environmental markers in males and females.

	Men n = 3571		Women n = 3179	
	OR (95% IC)	p	OR (95% IC)	p
BMI > 25 kg/m^2				
Biochemical markers				
HTG	4.9 (4.1–5.8)	<0.001	2.60 (2–3.3)	<0.001
Low HDL-C	2 (1.7–2.4)	<0.001	2.10 (1.7–2.5)	<0.001
High cholesterol	2.9 (2.3–3.7)	<0.001	1.30 (0.98–1.8)	0.24
Glucose	0.596 (0.45–0.78)	0.378	0.80 (0.352–1.23)	0.306
Environmental factors				
Alcohol consumption	1.2 (0.854–1.71)	0.284	0.98 (0.702–1.39)	0.945
Smoke	1.1 (0.733–1.3)	0.941	1.01 (0.664–1.56)	0.935
Sedentarism	1.1 (0.839–1.5)	0.377	2.3 (1.497–3.681)	<0.001
Mild food insecurity	0.912 (0.697–1.1)	0.501	1.5 (1.2–2.0)	<0.001
Insulin resistance				
Anthropometric parameters				
High body fat	6.8 (2.02–22.8)	0.002	3.86 (1.48–10.07)	0.006
BMI	3.6 (2.7–4.9)	<0.001	4.40 (3.2–6.3)	<0.001
WHR	4.6 (2.94–7.39)	<0.001	1.93 (1.29–2.88)	<0.001
WHI	3.5 (2.6–4.7)	<0.001	3.60 (2.6–5.1)	<0.001
Waist circumference	4.7 (3.4–6.3)	<0.001	3.7 (2.6–5.2)	<0.001
Biochemical markers				
HTG	2.5 (2.22–4-06)	<0.001	2.46 (1.6–3.79)	< 0.001
Low HDL-C	2.05 (1.46–2.88)	<0.001	1.78 (1.23–2.57)	< 0.001
High cholesterol	0.475 (0.31–0.71)	<0.001	0.391 (0.23–0.66)	0.908
Glucose	4.02 (2.53–6.37)	<0.001	2.67 (1.41–4.8)	0.002
Environment factors				
Alcohol consumption	1.3 (0.71–2.6)	0.334	1.7(1.08–2.77)	0.021
Sedentary	1.3 (0.172–0.88)	0.172	1.7 (1.1–2.6)	0.001
Smoke	0.786 (0.41–1.5)	0.467	1.4 (0.839–2.3)	0.195
Mild food insecurity	0.608 (0.33–1.1)	0.105	1.8 (0.08–3.07	0.201

Body fat >30% for women and >20% for men; BMI > 25.5 kg/m^2 (body mass index); WHR >0.85 for women and >0.94 for men (waist to hip ratio); WHI > 0.5 (waist to height index); waist circumference >80 cm for women and >90 cm for men. Logistic regression adjusted for age ($p \leq 0.05$).

Table 3
General characteristics of the sub sample for genetic analysis.

	Men N = 304			Women N = 361			Total N = 665			*p* Value
Age, y	19.3	±	2.0	19.2	±	1.70	19.2	±	1.9	0.047
Weight, Kg	70.9	±	13.5	59.7	±	12.0	64.9	±	13.9	0.001
Height, cm	171.4	±	6.8	159.8	±	6.3	165.2	±	8.7	0.001
BMI, kg/m^2	24.2	±	4.2	23.3	±	4.4	23.7	±	4.3	0.017
Waist, cm	84.1	±	11.1	77.9	±	11.3	80.8	±	11.6	0.001
Hip, cm	97.2	±	8.5	96.4	±	8.9	96.7	±	8.8	0.210
WHR	0.86	±	0.06	0.80	±	0.06	0.83	±	0.07	0.001
WHI	0.49	±	0.06	0.48	±	0.07	0.48	±	0.06	0.454
Total body fat, %	21.7	±	7.0	31.1	±	7.7	26.8	±	9.0	0.001
Glucose, mg/dL	85.1	±	9.0	82.2	±	8.9	83.5	±	9.1	0.001
Triglycerides, mg/dL	118.0	±	77.5	94.9	±	52.2	105.4	±	65.9	0.001
Cholesterol, mg/dL	157.8	±	28.6	157.1	±	13.3	157.4	±	30.9	0.756
HDL-C, mg/dL	47.8	±	10.9	53.5	±	13.3	50.9	±	12.6	0.001
LDL-C, mg/dL	86.7	±	25.2	84.1	±	23.1	85.2	±	24.1	0.179
Insulin, ug/mL	7.9	±	5.2	8.0	±	6.3	8.0	±	5.8	0.801
HOMA-IR	1.7	±	1.2	1.6	±	1.3	1.6	±	1.2	0.711

BMI: Body Mass Index; HWI: hip waist index; WHI: waist height index; TG: Triglycerides; Chol: Cholesterol; HDL-high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance. Values are shown as the mean ± SD. *P* value ($p \leq 0.05$) of Student's test for the difference of means between and women.

sumption and 69.4% reported high alcohol consumption (at least once a week), which was higher in men than in women at 76.2% and 62.3%, respectively. Six out of 10 young people did not practice any type of physical activity.

Association analyses (Table 2)

Association with BMI showed a similar risk between men and women for low HDL-C concentration, but for high triglycerides and cholesterol, the risk increased almost twice in men in comparison to women and no risk was associated with high levels of glucose. High triglycerides and a low level of HDL-C were relevant for both sexes and total cholesterol concentration was only associated with obesity in men. An association between sedentary lifestyle and mild food insecurity was only observed in women. Regarding IR, all anthropometric parameters and body composition were strongly associated with the risk of developing IR. High body fat percentage was associated with IR with an OR of 6.8 (2.02–22.8) for males and 3.86 (1.48–10.07) for females. Sedentarism also showed association for IR risk only for females.

The general characteristics of the subsample for the genetic analysis are shown in Table 3, where all anthropometric parameters

Table 4
Genotypic and allelic frequencies of the genetic variants.

	ABCA1(rs9282541)	APOAV(rs964184)	GCKR(rs1260326)
Allele	A	G	T
MAF	0.12	0.35	0.34
Genotypic frequency (%)	G/G: 76.7 A/G: 19.1 A/A: 2.7	C/C: 42.4 C/G: 43.7 G/G: 12.4	C/C: 44.9 C/T: 42.0 T/T: 13.1
Frequency of combined genetic variants (%)			
No risk genetic variant	16.2		
ABCA1 + APOAV	14.3		
ABCA1 + GCKR	12.1		
APOAV + GCKR	31.1		
ABCA1 + APOAV + GCKR	7.1		

MAF, minor allele frequency.

except hip circumference were different between men and women. Regarding biochemical markers, differences were observed for glucose, triglycerides and HDL-C. The allelic and genotypic frequencies of the analyzed genetic variants are shown in Table 4. The allele frequency of the risk of the three analyzed variants were 41.1% with at least one risk variant, 35.6% presented two risk variants and 7.1% presented all three risk variants. Together, the APOAV and GCKR variants showed the highest prevalence (31.1%).

We estimated the effect that the presence of one or two copies of the risk allele for each genetic variant has over the outcome. To perform this estimation, we created a binomial variable for each genetic variant where the first category is "minor allele carrier", defined as the combination of heterozygotes and homozygotes for the risk allele (minor allele), and the reference category is the "non carrier" set of patients, who had two copies of wild-type (non risk or major) allele. Participants with at least one risk allele were include in the analysis, that means that were included those with one, two or three genetic variants. Risk calculation was determined against participants that did not present any risk allele. Table 5 shows that a significant association was found between the risk allele for rs9282541 (ABCA1) variant and obesity, with a lower concentration of HDL-C and, in a minor way, with metabolic syndrome. For the rs964184 (APOAV) and rs1260326 (GCKR) variants, there were no significant associations with obesity. A positive association between the risk allele for the rs1260326 (GCKR) variant with high levels of glucose (>100 mg/dL) and insulin resistance was found. This association disappeared when the adjustment was made only by age and sex. For the APOAV variant, association was significant for high triglycerides, low HDL-C and metabolic syndrome. The ABCA1 and APOAV variants were significantly associated with metabolic syndrome. However, there was no significant association with the GCKR variant. We found that the subjects with rs9282541 AG/AA and rs964184 CG/GG genotypes showed a higher risk of MS (OR = 2.06, 95% CI = 1.024.17, p = 0.043) and (OR = 2.87, 95% CI = 1.29–6.40, p = 0.009), respectively, but not for IR with respect to the subjects with GG and CC genotypes. SNP–environment interaction with IR was relevant for subjects with rs9282541 AG/AA, rs964184 CG/GG and rs1260326 CT/TT with a BMI >25 or a high body fat percentage, but not with a sedentary lifestyle and sugar intake (Table 6).

Discussion

Several studies have shown that young people are vulnerable to metabolic disorders such as obesity, DM2, cardiovascular diseases, among others; which often are imperceptible and asymptomatic [18]. In this study, we were able to observe the metabolic status of Mexican young adults. Interestingly, despite having an adequate BMI, similarly to with a previous study [19], 5 out of 10 young people (49%) presented body fat above the recommended parameters (53% in men and 45% in women). This risk factor is related to the development of IR and cardiovascular disease [20]. Several studies have related a high percentage of fat, mainly visceral, with IR and DM2 [21]. In people with obesity, insulin concentrations were elevated, and much has been speculated about whether this is the cause or effect of IR. In this sense, several authors agree that, on the one hand, obesity induces IR by inflammatory factors and, on the other hand, the increase in insulin levels induces adipogenesis, which reflects a complex feedback circle that does not allow full deciphering of the etiology of both conditions [22].

Waist circumference is one of the main anthropometric parameters related to cardiovascular diseases risk [23]. In this study, 24% of young people showed a waist circumference above the recommended parameters of the International Diabetes Federation, 26% in women and 22% in men. Although BMI has been a very popular anthropometric parameter in clinical practice, in this research, it was observed that waist to height and waist to hip ratios were also good predictors of risk for IR.

Environmental factors are highly related to obesity, mainly prolonged fasting, a sedentary lifestyle, food insecurity and consumption of carbonated and/or sugared beverages [24]. In this sense, we found that males presented more risk factors than females, mainly related to DM2. A recent study showed that men, regardless of ethnicity, had a higher prevalence of diabetes compared with women of a similar age, BMI, socio-economic status and lifestyle factors, such as physical activity and eating habits [25]. However, in this study, it was observed that sedentarism and mild food insecurity were only associated with BMI for women.

Regarding biochemical parameters, a high prevalence of high triglycerides, low HDL-C and IR were found. These results agree with the national health and nutrition survey (ENSANUT) in a similar age group [26]. The biochemical parameters that were mostly associated with IR were triglycerides above 150 mg/dL and glucose above 100 mg/dL. These results are similar to those reported in other studies in a Mexican population of a different age range [27] and a Mexican population in the same age range [28].

ABCA1 plays a key role in cholesterol efflux and transfer from peripheral cells to lipid-poor apolipoprotein A1 [29]. SNP rs9282541, apparently exclusive to native American individuals, was associated with low HDL-C levels, obesity and DM2 in Mexican mestizos [30]. In this study, it was associated with low HDL-C and conferred significant susceptibility to metabolic syndrome (OR = 2.06 95%, C.I. = 1.02–4.17, p = 0.043). It has been reported that a dysfunction of the ABCA1 gene in adipocytes causes cholesterol accumulation, a decrease in the lipolysis and an increase in adipose tissue, thus producing glucose intolerance and insulin resistance [31]. In this study, R230C was the only variant related to obesity. (OR = 3.0 95%C.I. = 1.73–5.44, p = <0.001).

SNPs of APOAV are associated with dyslipidemia [32] and specifically with increased TG levels [7] for Mexican mestizos and

Table 5
Genetic variants and their association with metabolic parameters.

Gene	Genotype	Control	HTG	Control	Low HDL-C	Control	Glucose	Control	HOMA-IR	Control	Obesity	Control	MS IDF
		(n = 531)	(n = 134)	(n = 423)	(n = 242)	(n = 646)	(n = 19)	(n = 517)	(n = 88)	(n = 608)	(n = 57)	(n = 628)	(n = 37)
	GG	421 (79.3%)	97 (72.3%)	342 (80.7%)	175 (72.3%)	504 (78.0%)	14 (73.7%)	404 (78.1%)	63 (71.6%)	485 (79.8%)	32 (56.1%)	494 (78.7%)	24 (64.9%)
	AG	96 (18.1%)	33 (24.7%)	73 (17.2%)	56 (23.1%)	124 (19.2%)	5 (26.3%)	99 (19.1%)	23 (26.1%)	108 (17.8%)	21 (36.8%)	117 (18.6%)	12 (32.4%)
rs9282541 (ABCA1)	AA	14 (2.7%)	4 (3%)	8 (1.9%)	11 (4.5%)	18 (2.8%)	0 (0.0%)	14 (2.7%)	2 (2.3%)	15 (2.5%)	4 (7.0%)	17 (2.7%)	1 (2.7%)
	OR (CI)	1.42 (0.92–2.21)		1.79 (1.21–2.65)		1.24 (0.43–3.53)		1.23 (0.72–2.10)		3.07 (1.73–5.44)		2.06 (1.02–4.17)	
	p	0.112		**0.003**		0.686		0.438		**<0.001**		**0.043**	
	CC	244 (46.0%)	42 (31.4%)	202 (47.6%)	84 (34.7%)	276 (42.7%)	10 (52.6%)	226 (43.7%)	34 (38.6%)	260 (42.8%)	26 (45.6%)	278 (44.3%)	8 (21.6%)
	CG	228 (42.9%)	67 (50%)	170 (40.1%)	125 (51.7%)	286 (44.3%)	9 (47.4%)	223 (43.1%)	46 (52.3%)	270 (44.8%)	24 (42.1%)	271 (43.2%)	24 (64.9%)
rs964184 (APOAV)	GG	59 (11.1%)	25 (18.6%)	51 (12.0%)	33 (13.6%)	84 (13.0%)	0 (0.0%)	68 (13.2%)	8 (9.1%)	78 (12.8%)	7 (12.3%)	79 (12.6%)	5 (13.5%)
	OR (CI)	1.89 (1.26–2.84)		1.74 (1.24–2.44)		0.67 (2.69–1.67)		1.09 (0.67–1.77)		0.88 (0.50–1.53)		2.87 (1.29–6.40)	
	p	**<0.001**		**<0.001**		0.393		0.712		0.658		**0.009**	
	CC	246 (46.3%)	53 (39.5%)	193 (45.5%)	105 (43.4%)	286 (44.3%)	13 (68.4%)	226 (43.7%)	48 (54.5%)	272 (44.7%)	26 (45.6%)	281 (44.7%)	18 (48.6%)
	CT	230 (43.3%)	50 (37.3%)	179 (42.2%)	101 (41.7%)	275 (42.6%)	5 (26.3%)	223 (43.1%)	31 (35.2%)	254 (41.8%)	26 (45.6%)	267 (42.5%)	13 (35.1%)
rs1260326 (GCKR)	TT	55 (10.4%)	31 (n = 23.3%)	51 (12.0%)	36 (14.9%)	85 (13.2%)	1 (5.3%)	68 (13.2%)	9 (10.2%)	82 (13.5%)	5 (8.8%)	80 (12.7%)	6 (16.2%)
	OR (CI)	0.76 (0.51–1.13)		0.923 (0.66–1.28)		2.99 (1.13–7.87)		1.56 (0.98–2.47)		0.93 (0.54–1.62)		0.84 (0.43–1.64)	
	p	0.182		0.631		**0.027**		0.056		0.818		0.618	

Odds ratio and 95% CI were determined for the dominant model of the minor allele, logistic regression adjusted for age and sex ($p \leq 0.05$). Bold values means statistically significant differences.

Table 6
Association of gene–environment interactions with insulin resistance.

		BMI >25	p	% HBF >33	p	Sedentarism	p	Sugar intake	p
ABCA1	OR	3.73	<0.001	3.68	<0.001	0.92	0.865	0.98	0.969
(rs9282541)	(CI)	(2.01–6.91)		(2.03–6.68)		(0.39–2.17)		(0.50–1.92)	
APOAV	OR	3.41	<0.001	3.55	<0.001	1.09	0.757	1.16	0.614
(rs964184)	(CI)	(2.10–5.54)		(2.19–5.75)		(0.63–1.89)		(0.65–2.06)	
GCKR	OR	1.87	0.016	1.68	0.039	0.93	0.824	0.63	0.116
(rs1260326)	(CI)	(1.12–3.13)		(1.02–2.77)		(0.52–1.68)		(0.35–1.12)	

BMI; body mass index, %HBF; high body fat percentage. Analysis for different types of interaction by using logistic regression. Data adjusted for age and sex, ($p \leq 0.05$).

native American. The minor allele frequency of rs964184 was 0.35, which is similar to that reported for Mexican mestizos (0.38) and higher than the frequency reported for Europeans (0.12) [33]. We found that it was significantly associated to HTG (OR 1.89; 95%CI 1.26–2.84; p = <0.001) and hypoalphalipoproteinemia (OR 1.74; 95%CI 1.24–2.44; p = <0.001), similarly to the results reported for the Hispanic population [32].

Abdominal obesity is associated with elevated TG and low HDL levels so it has been seen that the variants of APOAV and its relationship with obesity are closely related to the metabolic profile of individuals [34]. In the present study, participants with a BMI > 25 and a high fat percentage showed associations with insulin resistance. These results agree with a study conducted in young people that showed that APOAV gene variants occurred more frequently in patients with metabolic syndrome and abdominal obesity [35]. Variant rs964184 (APOAV) also was associated with a significantly increased risk of metabolic syndrome among females but not in males (OR = 2.40, 95%, C.I. = 1.63–32.61, p = 0.008).

GCKR is a gene involved in the regulation of carbohydrates and lipids metabolism, the allelic variant for the rs1260326 of GCKR gene was associated with protection against DM2 in Mexican Amerindians and with hypertriglyceridemia in Mexican mestizos [36]. In this study, there was no association with hypertriglyceridemia, but association was observed with IR when adjusted by age, sex, and triglycerides and this association only disappeared when adjusted by age and sex. Another study has shown that the rs1260326 variant was associated with fatty liver and elevated triglycerides obese children and adolescents, regardless of age, BMI and glucose [37].

We demonstrated that SNPs in APOAV and ABCA1 were significantly associated with MS and its components in this population. It is notable that SNPs rs964184 (APOAV), rs9282541 (ABCA1) and rs1260326 (GCKR) alone do not confer a risk of insulin resistance, but the presence of these combined with a BMI > 25 and a high body fat promotes the presence this disorder. Therefore, it was observed that the environment–gene interaction can play a very important role in the development of insulin resistance directly linked to lifestyle and is accompanied by diseases such as diabetes and abdominal obesity. These factors are added to the effects of predisposition given by genetic variants [38].

In this study, it was possible to determine that most of the studied genetic variants were related to high concentrations of triglycerides and low concentrations of HDL-C. The genetic findings show that 42.7% of the studied population had two or three genetic variants associated with NCD. Identifying the presence of this variant in this population could be adding to the environmental and metabolic risk factors for the development of insulin resistance.

In conclusion, our results show that young adults in Mexico exhibited metabolic alterations that were related to non-communicable diseases that have an important impact on public health. These genetic findings suggest that this population is susceptible to the development of obesity, IR and MS. Early care strategies must be considered in the prevention of diseases.

Conflict of interest

Authors have no conflict of interest.

Ethical statement

The study was approved by the Bioethics Committee of the Natural Science Faculty of the Autonomous University of Queretaro under the guidelines of the declaration of Helsinki. All participants signed an informed consent before starting.

Acknowledgments

The authors acknowledge to *SU-Salud* program for all the facilities, the financial support of FOFI-UAQ 2016 and APIN-INSK 2017 and to CONACYT for KLFV fellowship.

References

[1] Organisation mondiale de la santé. Global Status Report on Noncommunicable Diseases 2014: Attaining the Nine Global Noncommunicable Diseases Targets; A Shared Responsibility. Geneva: World Health Organization; 2014.
[2] Enfermedades no transmisibles. World Health Organ n.d. http://www.who.int/es/news-room/fact-sheets/detail/noncommunicable-diseases. (Accessed 4 July 2018).
[3] DeMenna J, Puppala S, Chittoor G, Schneider J, Kim JY, Shaibi GQ, et al. Association of common genetic variants with diabetes and metabolic syndrome related traits in the Arizona Insulin Resistance registry: a focus on Mexican American families in the Southwest. Hum Hered 2014;78:47–58, http://dx.doi.org/10.1159/000363411.
[4] Srikanthan K, Feyh A, Visweshwar H, Shapiro JI, Sodhi K. Systematic review of metabolic syndrome biomarkers: a panel for early detection, management, and risk stratification in the West Virginian population. Int J Med Sci 2016;13:25–38, http://dx.doi.org/10.7150/ijms.13800.
[5] Paneni F, Costantino S, Cosentino F. Insulin resistance, diabetes, and cardiovascular risk. Curr Atheroscler Rep 2014;16:419, http://dx.doi.org/10.1007/s11883-014-0419-z.
[6] serrano rios M, Ascaso J, Blázquez E, Cabezas Cerraro J, Carmena R, Jimenez F, et al. Insulin resistance and its involvement in multiple risk factors associated with type 2 diabetes mellitus. Med Clínica 2002;119:458–63.
[7] Li X, Monda KL, Göring HHH, Haack K, Cole SA, Diego VP, et al. Genome-wide linkage scan for plasma high density lipoprotein cholesterol, apolipoprotein A-1 and triglyceride variation among American Indian populations: the strong heart family study. J Med Genet 2009;46:472–9, http://dx.doi.org/10.1136/jmg.2008.063891.
[8] Groop L, Forsblom C, Lehtovirta M, Tuomi T, Karanko S, Nissén M, et al. Metabolic consequences of a family history of NIDDM (the Botnia study): evidence for sex-specific parental effects. Diabetes 1996;45:1585–93.
[9] Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, et al. Biological, clinical, and population relevance of 95 loci for blood lipids. Nature 2010;466:707–13, http://dx.doi.org/10.1038/nature09270.
[10] Masic I, Hodzic A, Mulic S. Ethics in medical research and publication. Int J Prev Med 2014;5:1073–82.
[11] Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381–95, http://dx.doi.org/10.1249/01.MSS.0000078924.61453.FB.
[12] Pérez-Escamilla R. Escala Latinoamericana y Caribeña de Seguridad Alimentaria (ELCSA) — Manual de uso y aplicación, 9; 2007. p. 117–34.
[13] Bosy-Westphal A, Schautz B, Later W, Kehayias JJ, Gallagher D, Müller MJ. What makes a BIA equation unique? Validity of eight-electrode multifrequency BIA to estimate body composition in a healthy adult population. Eur J Clin Nutr 2013;67(Suppl. 1):S14–21, http://dx.doi.org/10.1038/ejcn.2012.160.
[14] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function

from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.
[15] National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004;114:555–76.
[16] Murguía-Romero M, Jiménez-Flores JR, Méndez-Cruz AR, Sigrist-Flores SC, Villalobos-Molina R. Insulin and HOMA-IR in healthy young Mexicans: a cut-off points proposal. Intern Med Open Access 2014:01, http://dx.doi.org/10.4172/2165-8048.S6-001.
[17] Grundy SM, Bryan H, Brewer J, Cleeman JI, Sidney C, Smith J, Lenfant C. Definition of Metabolic Syndrome. Arterioscler Thromb Vasc Biol 2004;24(2):e13–8, http://dx.doi.org/10.1161/01.ATV.0000111245.75752.C6.
[18] Brandão AP, Magalhães ME, Pozzan R, Brandão AA. Síndrome metabólico en jóvenes: diagnóstico y tratamiento. Rev Esp Cardiol 2005;58:3–13.
[19] Hung S-P, Chen C-Y, Guo F-R, Chang C-I, Jan C-F. Combine body mass index and body fat percentage measures to improve the accuracy of obesity screening in young adults. Obes Res Clin Pract 2017;11:11–8, http://dx.doi.org/10.1016/j.orcp.2016.02.005.
[20] Poyrazoglu S, Bas F, Darendeliler F. Metabolic syndrome in young people. Curr Opin Endocrinol Diabetes Obes 2014;21:56–63, http://dx.doi.org/10.1097/01.med.0000436414.90240.2c.
[21] Patel P, Abate N. Body fat distribution and insulin resistance. Nutrients 2013;5:2019–27, http://dx.doi.org/10.3390/nu5062019.
[22] Erion KA, Corkey BE. Hyperinsulinemia: a cause of obesity? Curr Obes Rep 2017;6:178–86, http://dx.doi.org/10.1007/s13679-017-0261-z.
[23] Benmohammed K, Valensi P, Benlatreche M, Nguyen MT, Benmohammed F, Pariès J, et al. Anthropometric markers for detection of the metabolic syndrome in adolescents. Diabetes Metab 2015;41:138–44, http://dx.doi.org/10.1016/j.diabet.2014.07.001.
[24] Vilchis-Gil J, Galván-Portillo M, Klünder-Klünder M, Cruz M, Flores-Huerta S. Food habits, physical activities and sedentary lifestyles of eutrophic and obese school children: a case–control study. BMC Public Health 2015;15:124, http://dx.doi.org/10.1186/s12889-015-1491-1.
[25] Ferguson TS, Younger-Coleman NOM, Tulloch-Reid MK, Hambleton IR, Francis DK, Bennett NR, et al. Educational health disparities in cardiovascular disease risk factors: findings from Jamaica Health and Lifestyle Survey 2007–2008. Front Cardiovasc Med 2017;4, http://dx.doi.org/10.3389/fcvm.2017.00028.
[26] Encuesta Nacional de Salud y Nutrición 2012. Resultados por entidad federativa y Nutrición 2012. Resultados por entidad federativa n.d. https://www.insp.mx/produccion-editorial/novedades-editoriales/3057-ensanut2012-resultados-entidad-federativa.html. (Accessed 4 July 2018).
[27] Pereira MA, Jacobs DR, Van Horn L, Slattery ML, Kartashov AI, Ludwig DS. Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the CARDIA study. JAMA 2002;287:2081–9.
[28] Salas R, Bibiloni M del M, Ramos E, Villarreal JZ, Pons A, Tur JA, et al. Metabolic syndrome prevalence among Northern Mexican adult population. PLoS One 2014;9:e105581, http://dx.doi.org/10.1371/journal.pone.0105581.
[29] Oram JF, Vaughan AM. ATP-Binding cassette cholesterol transporters and cardiovascular disease. Circ Res 2006;99:1031–43, http://dx.doi.org/10.1161/01.RES.0000250171.54048.5c.
[30] Acuña-Alonzo V, Flores-Dorantes T, Kruit JK, Villarreal-Molina T, Arellano-Campos O, Hünemeier T, et al. A functional ABCA1 gene variant is associated with low HDL-cholesterol levels and shows evidence of positive selection in Native Americans. Hum Mol Genet 2010;19:2877–85, http://dx.doi.org/10.1093/hmg/ddq173.
[31] Babashamsi MM, Koukhaloo SZ, Halalkhor S, Salimi A, Babashamsi M. ABCA1 and metabolic syndrome; a review of the ABCA1 role in HDL-VLDL production, insulin-glucose homeostasis, inflammation and obesity. Diabetes Metab Syndr 2019;13:1529–34, http://dx.doi.org/10.1016/j.dsx.2019.03.004.
[32] Aguilar-Salinas CA, Tusie-Luna T, Pajukanta P. Genetic and environmental determinants of the susceptibility of Amerindian derived populations for having hypertriglyceridemia. Metabolism 2014;63:887–94, http://dx.doi.org/10.1016/j.metabol.2014.03.012.
[33] Weissglas-Volkov D, Aguilar-Salinas CA, Nikkola E, Deere KA, Cruz-Bautista I, Arellano-Campos O, et al. Genomic study in Mexicans identifies a new locus for triglycerides and refines European lipid loci. J Med Genet 2013;50:298–308, http://dx.doi.org/10.1136/jmedgenet-2012-101461.
[34] Evans D, Buchwald A, Beil FU. The single nucleotide polymorphism -1131T&C in the apolipoprotein A5 (APOA5) gene is associated with elevated triglycerides in patients with hyperlipidemia. J Mol Med Berl Ger 2003;81:645–54, http://dx.doi.org/10.1007/s00109-003-0465-4.
[35] Zaki M, Amr K. Apolipoprotein A5 T-1131C variant and risk for metabolic syndrome in obese adolescents. Gene 2014;534:44–7, http://dx.doi.org/10.1016/j.gene.2013.10.032.
[36] Cid-Soto MA, Martínez-Hernández A, García-Ortíz H, Córdova EJ, Barajas-Olmos F, Centeno-Cruz F, et al. Gene variants in AKT1, GCKR and SOCS3 are differentially associated with metabolic traits in Mexican Amerindians and Mestizos. Gene 2018;679:160–71, http://dx.doi.org/10.1016/j.gene.2018.08.076.
[37] Santoro N, Zhang CK, Zhao H, Pakstis AJ, Kim G, Kursawe R, et al. A Variant in the Glucokinase Regulatory Protein (GCKR) gene is associated with fatty liver in obese children and adolescents. Hepatol Baltim Md 2012;55:781–9, http://dx.doi.org/10.1002/hep.24806.
[38] Ramasamy I. Update on the molecular biology of dyslipidemias. Clin Chim Acta Int J Clin Chem 2016;454:143–85, http://dx.doi.org/10.1016/j.cca.2015.10.033.