Sultan Qaboos University Med J, August 2018, Vol. 18, Iss. 3, pp. e291–298, Epub. 19 Dec 18
Submitted 31 Jan 18
Revision Req. 25 Feb 18; Revision Recd. 13 Mar 18
Accepted 5 Apr 18

doi: 10.18295/squmj.2018.18.03.005

CLINICAL & BASIC RESEARCH

Correlation of the Homeostasis Model Assessment Index and Adiponectin, Leptin and Insulin Levels to Body Mass Index-Associated Gene Polymorphisms in Adolescents

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العلاقة بين مَنْسِب تقييم نموذج الاستباب ومستويات الأديبونيكتن واللبتين والأنسولين ومنسب كتلة الجسم المرتبط بتعدد الأشكال الجينية عند المراهقين

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ABSTRACT: ***Objectives:*** This study aimed to describe correlations between glucose, insulin and adipokine levels and the homeostasis model assessment (HOMA) index with regards to the presence/absence of *fat mass and obesity-associated* (*FTO*) rs9939609 and *peroxisome proliferator-activated receptor* (*PPAR*)-*y* rs1801282 single nucleotide polymorphisms (SNPs) as indicators of body mass index in adolescents. ***Methods:*** This cross-sectional study was conducted between September and December 2016 in Toluca, Mexico. A total of 71 students between 14–18 years old were included. Various anthropometric and laboratory measurements were collected, including lipid profile, glucose, insulin and adipokine levels and HOMA index. The degree of association between variables was evaluated with regards to the presence/absence of the SNPs. ***Results:*** Leptin levels were significantly higher among female students ($P = 0.001$), although adiponectin levels did not differ significantly ($P = 0.060$). There were significant positive correlations between insulin levels and HOMA index with *FTO* ($r = 0.391$; $P = 0.007$ and $r = 0.413$; $P = 0.005$, respectively) and *PPARγ* ($r = 0.529$; $P = 0.007$ and $r = 0.537$; $P = 0.007$, respectively) SNPs. Leptin showed a significant positive correlation in the presence of *PPARγ* ($r = 0.483$; $P = 0.007$) or in the absence of both SNPs ($r = 0.627$; $P = 0.039$). However, adiponectin was significantly negatively correlated in the presence of *FTO*, either alone ($r = −0.333$; $P = 0.024$) or in combination with *PPARγ* ($r = −0.616$; $P = 0.043$). ***Conclusion:*** The presence of *FTO* and/or *PPARγ* SNPs might be related to a genetic predisposition to metabolic syndrome.

Keywords: Obesity; Body Mass Index; Single Nucleotide Polymorphisms; Fat Mass and Obesity Associated Protein, Human; Peroxisome Proliferator-Activated Receptor gamma; Adipokines.

الملخص: الهدف: تصف هذه الدراسة العلاقات بين مستويات الجلوكوز والأنسولين والاديبونكتين، ومَنْسِب تقييم نموذج الاستباب لمعرفة وجود أو عدم وجود تعدد أشكال النوكليوتيدات المفردة لمورثات كتلة الدهن والسمنة (*PPARγ* rs1801282 و *FTO* rs9939609) بحسبانها مؤشرات لكتلة الجسم عند المراهقين. **الطريقة:** أجريت هذه الدراسة المستعرضة ما بين سبتمبر وديسمبر عام 2016م في تولوسا بالمكسيك، وشارك فيها 71 طالبا في عمر ما بين 18–14 عاما. وتم إجراء عدد من القياسات الأنثروبومترية والمختبرية شملت مستويات الدهون والجلكوز والأنسولين والأديبونيكتن ومَنْسِب تقييم نموذج الاستباب. وتم تقييم درجة العلاقة بين تلك المتغيرات نسبةً إلى وجود أو غياب تعدد في أشكال النوكليوتيدات المفردة. **النتائج:** كان مستوى تركيز اللبتين أعلى بصورة مُعْتَدٍّة عند الطالبات الإناث ($P = 0.001$)، غير أن مستوى الاديبونكتين لم يتغير بصورة مُعْتَدٍّة ($P = 0.060$). وكانت هنالك علاقات إيجابية بين مستويات الانسولين ومَنْسِب تقييم نموذج الاستباب وبين أشكال النوكليوتيدات المفردة لمورثات كتلة الدهن والسمنة ($P = 0.005$; $r = 0.413$ و $P = 0.007$; $r = 0.391$)، على التوالي)، و *PPARγ* ($P = 0.007$; $r = 0.537$ و $P = 0.007$; $r = 0.529$)، على التوالي)، وجد هناك علاقة طردية إيجابية لهرمون الليبتين بوجود *PPARγ* ($P = 0.007$; $r = 0.483$) أو في غياب شكلي النوكليوتيدات المفردة ($P = 0.039$; $r = 0.627$). غير أن مستوى الاديبونكتين كان يتناسب سلبيا مع وجود مورثات كتلة الدهن والسمنة، إما بمفرده ($P = 0.024$; $r = -0.333$) أو في وجود *PPARγ* ($P = 0.043$; $r = -0.616$). **الخلاصة:** يمكن أن يكون لوجود مورثات كتلة الدهن والسمنة و/أو أشكال النوكليوتيدات المفردة ل *PPARγ* علاقة بالاستعداد الوراثي للإصابة بالمتلازمة الأيضية (الاستقلابية).

الكلمات المفتاحية: السمنة؛ مؤشر كتلة الجسم؛ تعدد أشكال النوكليوتيدات المفردة؛ البروتين المرتبط بكتله الدهن والسمنة، إنْسان؛ PPARγ؛ الأديبوكاينز.

Advances in Knowledge

- *Certain single nucleotide polymorphisms (SNPs) have been associated with obesity and insulin resistance. However, current data are conflicting regarding the roles of the fat mass and obesity-associated (FTO) rs9939609 and peroxisome proliferator-activated receptor (PPAR)-y rs1801282 SNPs in this regard.*

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- *The current study found that certain adipokines were significantly correlated with FTO and PPARγ expression.*

Application to Patient Care

- *Determining the presence or absence of FTO and PPARγ SNPs among adolescents might help in the design and implementation of more intensive obesity prevention strategies in this population.*

Obesity is a multifactorial disease determined by a complex interaction between genetic and environmental factors. Previous research has associated an obesogenic phenotype with the presence of specific polymorphisms also linked to the development of insulin resistance, diabetes mellitus and metabolic syndrome.[1] Moreover, pancreatic function may be altered by mutations that cause changes in the activity or expression of proteins involved in the regulation of basal energy expenditure; the latter phenomenon is explained in part by the various mechanisms of oxidative phosphorylation. Although the effect of each individual gene or combination of different genetic variants on metabolism and thermogenesis is uncertain, this may explain why certain individuals have a greater tendency to develop metabolic disorders.[2]

In recent decades, efforts have intensified in the search for single nucleotide polymorphisms (SNPs) causing observed changes in the signalling pathways that regulate metabolic processes, leading to failures in energy homeostasis and predisposing individuals to diabetes and obesity.[3] Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptor proteins that function as transcription factors. These receptors are present in different metabolic pathways related to energy homeostasis, in addition to the lipid route. So far, three PPAR isoforms have been identified; the PPARγ isoform, which is highly expressed in white adipose tissue, is involved in lipid storage and energy dissipation and is recognised to be the master regulator of adipogenesis.[4] The *fat mass and obesity-associated* (*FTO*) gene is composed of nine exons on chromosome 16 (16q12.2).[5] It was the first gene to be associated with obesity in genome-wide association studies.[6] Frayling *et al*. observed that adults with the *FTO* rs9939609 SNP had a 1.67-fold increased risk of obesity and weighed an average of 3–4 kg more than those without this polymorphism.[7]

In Mexico, genomic studies have demonstrated several genetic ancestries for the local population.[8] However, this implies that there may be discrepancies in the role of some SNPs in the presence of obesity-related conditions, such as metabolic syndrome. This study aimed to identify correlations between glucose, insulin and adipokine levels and the homeostasis model assessment (HOMA) index with regards to the presence or absence of *FTO* rs9939609 and *PPARγ* rs1801282 SNPs as indicators of body mass index (BMI) in Mexican adolescents.

Methods

This cross-sectional study was conducted from September to December 2016 at the Autonomous University of Mexico State (UAEM) in Toluca, Mexico. All adolescents between 14–18 years old attending the Lic. Adolfo López Mateos Preparatory School in Toluca were invited to participate in the study. The exclusion criteria included a history of smoking, being pregnant or having been diagnosed with a chronic or acute disease. The sample size was calculated as follows:[9]

$$n = \frac{z^2 \times p(1\text{-}p)}{\varepsilon^2}$$

$$n' = \frac{n}{1 + \frac{z^2 \times p(1\text{-}p)}{\varepsilon^2 \, \mathrm{N}}}$$

where n is the infinite population of available participants (981 adolescents), z is the 95% confidence level (1.96), p is the estimated percentage of the studied polymorphisms in the total population (30%), ε is the margin of error set at 11% with a replacement rate of 9%, n' is the required finite sample size and N is the population size. Based on this, the required sample size was set at 68 adolescents.

A body composition monitor was used to measure the subjects' weight (BC-533 InnerScan Body Composition Monitor®, Tanita Corp., Tokyo, Japan), while a standard stadiometer was used to measure height. BMI was calculated as weight in kg divided by height in m^2. According to gender- and age-specific World Health Organization BMI classifications for adolescents, the participants were categorised as either normal, overweight (≥1 standard deviation [SD] of the z score) or obese (≥2 SD of the z score).[10] Waist and hip circumferences were measured using a fibreglass tape to the nearest 0.1 cm and waist-to-height and waist-to-hip ratios calculated accordingly. Blood pressure was checked by auscultation using a sphygmomanometer with an appropriately sized cuff. Systolic and diastolic hypertension was determined according to the criteria for high blood pressure in children and adolescents from the National High Blood Pressure Education Program Working Group.[11]

After a fasting period of 8 hours, 3 mL of venous blood were drawn from participants and collected into BD Vacutainer® tubes (Becton, Dickinson and Co., Franklin Lakes, New Jersey, USA). Using enzymatic methods, concentrations of glucose, uric acid, total cholesterol,

high-density lipoproteins (HDLs), low-density lipoproteins (LDLs) and triglycerides were determined according to the manufacturer's instructions for each reagent assay kit (Randox Laboratories Ltd., Crumlin, County Antrim, UK). The participants' thyroid profiles were measured by radioimmunoassay, whereas adiponectin, insulin and leptin levels were determined using the 900 series Invitrogen® enzyme-linked immunosorbent assay (Thermo Fisher Scientific Inc., Pittsburgh, Pennsylvania, USA). One sample remained frozen at -70 °C until DNA extraction. The atherogenic index of plasma (AIP) was calculated as total cholesterol divided by HDL. The HOMA index for insulin resistance was calculated as follows:[12]

$$HOMA\ index = \frac{fPI \times fPG}{22.5}$$

where fPI is fasting plasma insulin and fPG is fasting plasma glucose. A diagnosis of metabolic syndrome was based on the criteria of the International Diabetes Federation (IDF) and adjusted for age.[13]

DNA extraction was performed using the MagNA Pure LC 2.0 Instrument and MagNA Pure LC DNA Isolation Kit 1 (Roche Diagnostics GmbH, Manheim, Germany). Results were quantified using the N60 NanoPhotometer® (Implen GmbH, Munich, Germany), reporting the concentration (in µg/mL) and purity (the ratio of the absorbance of 260/280 nm). Genotyping was performed by polymerase chain reaction analysis in a Life ECO® thermal cycler (Bioer Technology Co. Ltd., Hangzhou, China). The primers and conditions for each polymorphism are listed in Table 1.[14] Oligonucleotides were designed using the PrimerQuest® web tool (Integrated DNA Technologies Inc., Skokie, Illinois, USA) and synthesised at the Institute of Biotechnology, National Autonomous University of Mexico, Cuernavaca, Morelos, Mexico. The Basic Local Alignment Search Tool® (National Library of Medicine, Bethesda, Maryland, USA) was used to verify the correct hybridisation. The final products were visualised in 2% agarose gel, stained with ethidium bromide and digitally documented using an ultraviolet transilluminator system (Gel Logic 212 Pro, Carestream Health, Rochester, New York, USA) [Figure 1]. Sequencing was performed at the National Institute of Genomic Medicine in Mexico City to confirm the detection of polymorphisms as per previously described methods.[14]

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), Version 19 (IBM Inc., Armonk, New York, USA). Descriptive continuous data were presented as means and SDs while qualitative variables were expressed as percentages. Either the Student's t-test or Mann-Whitney U test were used, depending on whether the variables were normally distributed. Using Pearson's correlation coefficient, the degree of association between glucose, insulin and adipokine levels, AIP and HOMA index were evaluated in two different settings, the first being the absence of either SNP and the second being the presence of either or both SNPs. Multivariate linear modelling was performed to establish the possible effect of the presence of polymorphisms and gender on lipid profile. A linear regression model weighted by gender was used to determine whether very-low-density lipoprotein (VLDL), LDL, HDL and triglyceride levels were predictors of HOMA index. A linear regression analysis was also used

Table 1: Primers and polymerase chain reaction conditions for the studied polymorphisms[14]

	Polymorphism	
	FTO	*PPARγ*
Accession number*	NG_012969.1	XM_011533843.2
Variant	rs9939609	rs1801282
Forward primer	tggctcttgaatgaatag-gattcagaa	ccaattcaagcccagtcctttc
Reverse primer	agcctctctaccatcttat-gtccaaaca	cagtgaaggaatcgctttccg
PCR conditions	Denaturation - 10 minutes at 95 °C 15 seconds at 95 °C 30 seconds at 60 °C 30 seconds at 72 °C } × 40 cycles Extension end cycle - 5 minutes at 72 °C	

FTO = fat mass and obesity-associated; PPAR = peroxisome proliferator-activated receptor; PCR = polymerase chain reaction.
**From the National Center for Biotechnology Information database.*

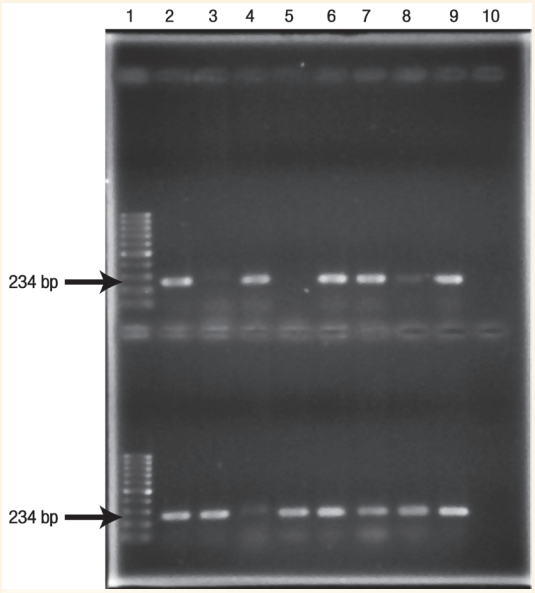

Figure 1: Agarose gel electrophoresis image of polymerase chain reaction amplification products showing the presence of a *fat mass and obesity-associated* (*FTO*) polymorphism. Lane one contains the molecular marker, lanes 2–8 contain amplified *FTO* gene DNA fragments, lane nine contains the positive control and lane 10 contains the negative control.

Table 2: Anthropometric and laboratory variables according to gender among adolescents in Toluca, Mexico (N = 71)

Variable	Mean ± SD			*P* value
	Total	Females (n = 40)	Males (n = 31)	
Age in years	15.7 ± 0.7	15.7 ± 0.7	15.8 ± 0.7	0.525
Height in m	1.63 ± 0.09	1.57 ± 0.06	1.70 ± 0.07	≤0.001
Weight in kg	65.8 ± 13.8	59.4 ± 9.6	74.0 ± 14.2	≤0.001
BMI in kg/m^2	24.5 ± 3.8	23.9 ± 3.8	25.3 ± 3.7	0.111
WHR	0.86 ± 0.06	0.84 ± 0.0	0.88 ± 0.06	0.006
Adiponectin in µg/nL	12.9 ± 4.4	13.8 ± 4.2	11.8 ± 4.4	0.060
Glucose in mg/dL	91.9 ± 6.4	90.7 ± 4.9	93.4 ± 7.8	0.079
Insulin in IU/mL	14.6 ± 8.3	14.5 ± 8.2	14.8 ± 8.5	0.899
HOMA index	3.03 ± 1.83	2.96 ± 1.7	3.11 ± 1.92	0.743
Cholesterol in mg/dL	168.9 ± 37.9	179.3 ± 40.2	156.0 ± 30.7	0.010
HDL in mg/dL	42.5 ± 10.7	45.7 ± 11.1	38.67 ± 8.9	0.006
Leptin in ng/mL	18.0 ± 1.6	23.3 ± 15.7	11.0 ± 14.0	0.001
LDL in mg/dL	107.1 ± 31.8	112.0 ± 34.0	100.9 ± 28.2	0.149
Triglycerides in mg/dL	131.8 ± 72.1	131.2 ± 63.3	132.5 ± 82.9	0.939
Uric acid in mg/dL	4.4 ± 1.4	3.6 ± 1.0	5.3 ± 1.3	≤0.001
VLDL in mg/dL	19.2 ± 12.2	21.5 ± 12.5	16.3 ± 11.3	0.080
AIP	4.0 ± 0.9	4.0 ± 1.0	4.1 ± 0.8	0.743

SD = standard deviation; BMI = body mass index; WHR = waist-to-hip ratio; HOMA = homeostatic model assessment; HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein; AIP = atherogenic index of plasma.

to test BMI as the dependent variable and age as the independent variable according to gender and weighted by the presence of polymorphisms. A *P* value of ≤0.050 was considered statistically significant.

This study was approved by the Institutional Review Board of the Medical Sciences Research Center at UAEM (#2015/14). All subjects and their parents/guardians provided informed consent prior to participation in the study. All of the study procedures were in line with the ethical standards of the revised Declaration of Helsinki as well as the Mexican Standard for the Implementation of Projects of Research for Health in Humans (#NOM-012-SSA3-2012).

Results

A total of 71 adolescents were included in the study, of which 40 (56.3%) were female and 31 (43.7%) were male. The mean age was 15.7 ± 0.7 years and the mean BMI was 24.5 ± 3.8 kg/m^2. Based on the IDF criteria, 21.1% of the subjects had metabolic syndrome.[13] Nevertheless, 56 adolescents (78.8%) were positive for at least one diagnostic criterion of metabolic syndrome, with high triglyceride levels being most frequently observed (52%). In terms of family history, 14 (19.7%) and 16 (22.5%) adolescents had a mother or father, respectively, with metabolic disease. Interesting, 39 adolescents (54.9%) had relatives affected by chronic disease; however, none of these individuals had been diagnosed with hypothyroidism.

According to gender, there was a statistically significant difference among the participants in terms of weight, height, waist-to-hip ratio and cholesterol, HDL, leptin and uric acid levels (*P* <0.050 each) [Table 2]. Age and leptin levels showed a non-parametric distribution. Although *FTO* SNPs were more frequent among females, this difference was not statistically significant (χ^2 = 2.4671; *P* = 0.116). Similarly, there was a non-significant increase in *PPARγ* SNP frequency among males (χ^2 = 1.2884; *P* = 0.256). There was no difference according to gender in terms of the presence of both SNPs (χ^2 = 0.2819; *P* = 0.595) [Table 3]. According to a linear regression analysis weighted by gender, VLDL, HDL, LDL and triglyceride levels significantly influenced HOMA index (*P* ≤0.001). Similar results were observed among adolescents with *FTO* or *PPARγ* SNPs (*P* = 0.002) as well as those without *PPARγ* polymorphisms (*P* = 0.035).

Table 3: Frequency of body mass index-related polymorphisms according to gender among adolescents in Toluca, Mexico (N = 71)

Polymorphism	n (%)			*P* value
	Total	Females (n = 40)	Males (n = 31)	
Neither *FTO* nor *PPARγ*	11 (15.5)	4 (10)	7 (22.6)	0.146
FTO alone	35 (49.3)	23 (57.5)	12 (38.7)	0.116
PPARγ alone	14 (19.7)	6 (15)	8 (25.8)	0.256
Both *FTO* and *PPARγ*	11 (15.5)	7 (17.5)	4 (12.9)	0.595

FTO = fat mass and obesity-associated; PPAR = peroxisome proliferator -activated receptor.

Overall, the *PPARγ* SNP was present in 25 adolescents (35.2%) and the *FTO* SNP was present in 46 (64.8%), including 11 cases (15.5%) in which both *PPARγ* and *FTO* SNPs were present. Neither SNP was present in 11 individuals (15.5%). Insulin levels and HOMA index were statistically correlated with the presence of *FTO* (P = 0.007 and 0.005, respectively), *PPARγ* (P = 0.007 each) and both SNPs combined (P = 0.039 and 0.029, respectively). While leptin showed a positive significant correlation in the presence of *PPARγ* (r = 0.483; P = 0.014) and in the absence of either SNP (r = 0.627; P = 0.039), adiponectin was significantly negatively correlated with *FTO*, either alone (r = –0.333; P = 0.024) or in combination with *PPARγ* (r = –0.616; P = 0.043) [Table 4]. A multivariate linear model showed that the presence of the SNPs were not determinants of BMI and lipid profile. However, the effect of gender was significant (P <0.050), particularly in the setting of both SNPs together (P = 0.021) [Table 5].

Discussion

Worldwide, various studies of different ethnic populations have shown conflicting results regarding the relationship between body weight and *FTO* and *PPARγ* polymorphisms. For example, the *PPARγ Pro12Ala* rs1801282 polymorphism has been associated with obesity and insulin resistance among Asian Indians; however, in a Chinese sample, it was reported to be a protective factor against type 2 diabetes and obesity.[15,16] Huang *et al*. found that the presence of the rs2282440-SDC3T/T genotype alongside the rs1801282 *PPARγ2* carrier genotype was strongly associated with obesity.[17] On the other hand, Queiroz *et al*. found that *PPARγ* rs1801282 conferred a higher risk of altered insulin levels and HOMA index for insulin resistance among overweight adolescents.[18] To some extent, the latter observation is consistent with the results of the present study.

A previous study demonstrated that circulating lipids in Mexican children modified the association between the *PPARγ2* rs1801282 genotype and insulin resistance.[19] In the current study, significant associations were noted between HOMA index and the presence of *FTO* or *PPARγ* polymorphisms, taking into account the role of lipids and weighted by gender. In Asiatic populations, *FTO* has been associated with an increased risk of obesity and type 2 diabetes.[20] Saldaña-Alvarez *et al*. found that *FTO* SNPs made differential contributions to obesity risk, supporting the hypothesis that mechanisms involving these variants are gender-dependent and that these changes may contribute to disease development.[21] Although the researchers evaluated different *FTO* SNPs (rs1121980, rs17817449, rs3751812, rs9930506 and rs17817449) to that of the present study (rs9939609), such findings confirm the possibility that gender is a risk

Table 4: Correlations between glucose, insulin and adipokine levels and homeostasis model assessment index with body mass index-related polymorphisms among adolescents in Toluca, Mexico (N = 71)

Variable	Polymorphisms							
	Neither *FTO* nor *PPARγ* (n = 11)		FTO (n = 46)*		*PPARγ* (n = 25)*		Both *FTO* and *PPARγ* (n = 11)	
	r	*P* value	r	*P* value	r	*P* value	r	*P* value
Glucose	0.303	0.365	0.272	0.070	0.090	0.675	0.292	0.413
Insulin	0.600	0.051	0.391	0.007	0.529	0.007	0.627	0.039
HOMA index	0.600	0.051	0.413	0.005	0.537	0.007	0.685	0.029
Leptin	0.627	0.039	0.248	0.096	0.483	0.014	0.221	0.513
Adiponectin	–0.323	0.332	–0.333	0.024	–0.110	0.599	–0.616	0.043
AIP	0.721	0.012	0.463	0.001	0.192	0.368	0.487	0.154

FTO = fat mass and obesity-associated; PPAR = peroxisome proliferator-activated receptor; HOMA = homeostasis model assessment; AIP = atherogenic index of plasma.

**Including the 11 adolescents with both polymorphisms.*

Table 5: Multivariate linear model for body mass index-related polymorphisms and gender as determinants for body mass index and lipid profile

Variable	Statistical test	Value*	F value	*P* value
FTO	Pillai's trace	0.066	1.027	0.401
	Wilks' lambda	0.934	1.027	0.401
	Lawley-Hotelling trace	0.071	1.027	0.401
	Roy's largest root	0.071	1.027	0.401
PPARγ	Pillai's trace	0.107	1.738	0.154
	Wilks' lambda	0.893	1.738	0.154
	Lawley-Hotelling trace	0.120	1.738	0.154
	Roy's largest root	0.120	1.738	0.154
Gender	Pillai's trace	0.162	2.797	0.034
	Wilks' lambda	0.838	2.797	0.034
	Lawley-Hotelling trace	0.193	2.797	0.034
	Roy's largest root	0.193	2.797	0.034
FTO × *PPARγ*	Pillai's trace	0.105	1.697	0.163
	Wilks' lambda	0.895	1.697	0.163
	Lawley-Hotelling trace	0.117	1.697	0.163
	Roy's largest root	0.117	1.697	0.163
FTO × gender	Pillai's trace	0.040	0.607	0.659
	Wilks' lambda	0.960	0.607	0.659
	Lawley-Hotelling trace	0.042	0.607	0.659
	Roy's largest root	0.042	0.607	0.659
PPARγ × gender	Pillai's trace	0.032	0.477	0.752
	Wilks' lambda	0.968	0.477	0.752
	Lawley-Hotelling trace	0.033	0.477	0.752
	Roy's largest root	0.033	0.477	0.752
FTO × *PPARγ* × gender	Pillai's trace	0.178	3.143	0.021
	Wilks' lambda	0.822	3.143	0.021
	Lawley-Hotelling trace	0.217	3.143	0.021
	Roy's largest root	0.217	3.143	0.021

FTO = fat mass and obesity-associated; PPARγ = peroxisome proliferator -activated receptor.

**The degrees of freedom of hypothesis and error were 4.000 and 58.000, respectively, for each value.*

factor for obesity.[17] Similarly, these results are supported by those of Huđek *et al.*, who found a statistically significant positive correlation between frequencies of high-risk *FTO* genotypes in obese women (AA rs9939609, CC rs1421085 and GG rs17817449).[22]

Díaz-Anzaldúa *et al.* reported that differences in mean BMI levels among Mexican patients with bipolar disorder were explained by the presence of *FTO* rs8050136 and rs9939609 genotypes.[23] Another study showed that the *locus* of the *FTO* gene was significantly associated with increased BMI in indigenous Mexican populations.[24] Muñoz-Yáñez *et al.* found that *FTO* rs9939609 polymorphisms were associated with obesity-related traits, including elevated BMI, cholesterol and LDL levels, tricep skinfolds and an increased waist circumference and waist-to-height ratio.[25] In the present study, an extremely high percentage of adolescents had *FTO* SNPs (64.8%). Given a population of approximately nine million Mexicans aged 15–20 years old, there are an estimated 5,830,200 young people with *FTO* rs9939609 polymorphisms and, therefore, a corresponding risk of obesity.[26]

Such findings are alarming for the local healthcare system. Fortunately, despite a genetic predisposition influenced by polymorphisms, obesity is a modifiable condition, even with a positive genetic profile risk score.[27] In the PREDIMED-NAVARRA randomised trial, *PPARγ Pro12Ala* rs1801282 carriers exhibited lower telomere shortening compared to those with the *Pro/Pro* genotype after five years of adherence to a Mediterranean-style diet.[28] Unfortunately, the molecular effects of a traditional Mexican diet have yet to be fully elucidated.

In the current study, mean HDL levels were significantly higher among females. However, this may be because the mean level for males was below recommendations reported for the Mexican population.[29] In addition, female students also had significantly higher leptin levels. Although leptin is a significant predictor of carotid *intima media* thickness, previous research has confirmed that men suffer from higher cardiovascular-related mortality compared to women.[30,31] Such findings undermine the epidemiological evidence for utilising leptin as a prognostic tool for cardiovascular disease in adolescents.

As in previous research, females in the current study also demonstrated significantly higher cholesterol levels.[32] A strong correlation has been established between cholesterol and visceral adipose tissue as quantified by dual-energy X-ray absorptiometry.[33] Unfortunately, this technique was not utilised in the present study. Finally, the frequency of metabolic disease among the parents of the studied adolescents was lower than expected; instead, students' relatives were found to have a high rate of chronic disease. However, it is unclear whether these individuals had lipid-related abnormalities.

It is worth noting that various researchers have recommended lowering BMI cut-off values for over-

weight and obese categories in Mexican and Asiatic populations.[34,35] Thus, if a BMI of ≥27 kg/m^2 were considered to indicate obesity, 31% of the adolescents in the current study would have been considered obese. Males were significantly heavier than females; this was accordingly reflected by slight elevations in glucose and insulin levels and HOMA index. However, these differences were not significant, possibly due to similarities in BMI in both genders. Therefore, further studies are recommended including other variables which could influence BMI in adolescents, such as physical activity and dietary habits.[36] Another limitation of this study was the small sample size; nevertheless, investigations regarding associations between polymorphisms and clinical parameters for metabolic syndrome or obesity can be clinically significant in small samples.[37]

Conclusion

The results of this study suggest significant positive correlations between insulin levels and HOMA index with BMI-related *FTO* rs9939609 and/or *PPARγ* rs180-1282 polymorphisms. Future epidemiological studies are recommended to determine the net causative effect of such gene variants so as to halt the development of a pandemic of obesity-related health problems. Although the main causes of obesity, diabetes and metabolic syndrome are lifestyle factors, the role of such polymorphisms could help to explain why some individuals have a greater tendency to develop metabolic disorders and are more resistant to weight control interventions than others.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FUNDING

This study was funded with the aid of a grant from the Mexican Ministry of Education (grant #PROMEP/2013/CA-186/103105/13/9057).

ACKNOWLEDGEMENTS

The preliminary version of this study was submitted as a M.Sc. thesis to the UAEM in 2016. This version is available on the university website.

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