Research article

ObRb, AdipoR1, and *CYP19* gene expression show significant association with obesity and overweight in healthy women

Jessica Berenice López González[1], Antonio Sandoval-Cabrera[3], Laura Sánchez Hernández[2,4], Enrique Morales Avila[1], Jonnathan Guadalupe Santillán Benítez[1]

Abstract

Obesity and overweight are diseases characterized by excessive accumulation of adipose tissue in the body and are defined as an increase in Body Mass Index (BMI) with values greater than 25 kg/m^2. Multiple causes of these increases in BMI have been reported. Some have been attributed to the expression of several genes involved in the leptin and adiponectin pathway as well as postmenopausal stage in women.

In this research, we focused on evaluating whether the expression of *ObRb, AdipoR1*, and *CYP19* genes have any association with the increase in BMI in the female population of Mexico City over 55 years of age. For this, we worked with a group of 45 women volunteers without the diagnosis of any confirmed pathology.

The study population was classified into three groups (average weight, overweight and obese) according to their BMI and was characterized according to their clinical data of blood cytometry and blood chemistry. At the same time, RT-PCR determined *ObRb, AdipoR1*, and *CYP19* gene expression.

1. Universidad Autónoma del Estado de México (UAEMex) Faculty of Chemistry. Department of Pharmacy, Toluca, México.

2. Universidad Autónoma del Estado de México (UAEMex), Faculty of Sciences. Department of Biotechnology, Toluca ,México.

3. High Specialty Laboratory in Hemato-Oncology, Hospital for the Child, Medical Institute of the State of Mexico, Toluca , México.

4. Instituto Politécnico Nacional. Interdisciplinary Professional Unit of Biotechnology, Department of Bioprocesses, Ciudad de México, México.

Corresponding autor:
Jonnathan Guadalupe Santillán Benítez
E-mail: jonnathangsb@yahoo.com.mx
ORCID: https://orcid.org/0000-0003-3574-1231

https://doi.org/10.22490/24629448.7532

Obtained results showed a moderate correlation (r=0.648, *p*=0.043) of *ObRb* gene expression in women with obesity and a moderate negative correlation (r= -0.389, *p*=0.034) *AdipoR1* gene in women with overweight or obesity.

Based on BMI data, more than 70 % of the study population was overweight and obese. Also, it was found that 64 % of the study population exceeded 150 mg/dL of triglycerides which is the normal healthy range.

Keywords: *ObRb, AdipoR1, CYP19*, body mass index, obesity, overweight.

Introduction

Obesity and overweight have spread rapidly throughout the world due to different dietary changes and the lack of physical activity and have become a public health crisis [1-2]. In Mexico, and according to the ENSANUT-INEGI (National Health and Nutrition Survey and National Institute of Statistics and Geography) in 2018, the percentage of adults with obesity was 36.1 % and overweight 39.1 %, respectively, placing Mexico as the second country with the second-highest prevalence rate in obesity and overweight [3-4].

Obesity and overweight are defined as a disease characterized by the excessive accumulation of adipose tissue in the body, presenting itself as a variation in the Body Mass Index (BMI) [5-6]. The BMI provides the most useful measure to identify a state of obesity or overweight, since it indicates the relationship between weight and height of an individual, a person is considered with obesity when his BMI is equal or higher than 30 kg/m^2 and overweight when his BMI is equal or higher than 25 kg/m^2 [7-8].

BMI increase is favored by the presence of postmenopausal stage in women, In Mexico the average age in which this stage varies is between 41 and 55 years, due to different changes in hormones and slow metabolism, as a result of estrogens and progesterone deficits which increase the risk of developing cardiovascular and metabolic diseases, diagnosis and the development of different types of cancer [9-13].

Obesity and overweight are related to several adverse effects, including developing metabolic and cardiovascular diseases and diagnosing and developing various types of cancer [9-13]. Several environmental and genetic factors influence the development of this pathology[14- 17]. Studies have reported that 50-70 % of BMI variations are attributable to genetic differences specific to everyone[18]. Currently, more than 127 genes associated with obesity have been reported,

among which the long leptin receptor gene (*ObRb*) and the *CYP19* gene coding for the aromatase enzyme stand out[19-21].

The long leptin receptor gene (*ObRb*) belongs to the cytokine family and regulates fat metabolism. So far, six isoforms of this receptor have been reported, being *ObRb* the active form, which is associated with the JAK2-STAT3 system and with other intracellular signaling cascades. It has been reported that a mutation or variation can affect its functionality, preventing it from binding to leptin or that upon binding, it cannot be activated, resulting in excessive hunger and weight gain [22-28].

The adiponectin type 1 receptor gene (*AdipoR1*) is a ubiquitously expressed transmembrane receptor with a high affinity for globular adiponectin, abundantly expressed in skeletal muscle. It is binding to adiponectin activates adenosine monophosphate-dependent protein kinase (AMPK), PPAR-γ, and mitogen-activated protein kinase (MAPK). Adiponectin increases insulin sensitivity through different signaling pathways, reduces hepatic glucose synthesis, and promotes fatty acid oxidation [29-31].

On the other hand, the *CYP19* gene coding for the aromatase enzyme is involved in the biosynthesis of estrogens, and aromatase inhibitors, it may affect the distribution and regulation of body fat by modulating the ratio of androgens to estrogens in adipose tissue and has been associated with obesity-related phenotypes in postmenopausal women [32-33].

Therefore, the present study aimed to determine whether the expression of the genes long leptin receptor (*ObRb*), adiponectin receptor type 1 (*AdipoR1*), and the gene coding for the enzyme aromatase (*CYP19*) were associated with BMI in Mexican women and could be used as predisposing factors for obesity and overweight.

Materials and methods

A total of 45 healthy female volunteers, older than 55 years of age without a confirmed diagnosis of any pathology and with the prior signature of informed consent were recruited. Patients diagnosed with some infectious-contagious disease were excluded as well as those who had a dyscrasia and took drugs from 24 to 48 hours prior to sampling. Patients who decided to leave the study on demand and voluntarily were eliminated as well as non processable, insufficient or noncompliant with the requested criteria blood samples. Data collection was performed following the research ethics guidelines of the participating hospital and the WMA Declaration of Helsinki 2013 [34].

BMI (Body Mass Index).

The determination of BMI was established through the weight-to-height ratio using the formula:

$$BMI = \frac{Weight(kg)}{Heightratio(m^2)}$$

To classify the study population, the recommended criteria by the WHO were used: average weight (BMI < 25 kg/m^2), overweight (BMI ≥ 25 kg/m^2), and obesity (BMI ≥ 30 kg/m^2) [7, 8].

Clinical information of biometric parameters

The participant's blood chemistry and the biometric parameters were performed to evaluate the levels of glucose, urea, creatinine, uric acid, total cholesterol, and triglycerides using spectrophotometry on the Beckman colter ADR7000 platform. Through blood cytometry, the number of leukocytes, neutrophils, lymphocytes, basophils, monocytes, eosinophils, erythrocytes, Hgb (Hemoglobin), Hto (Hematocrit), MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Hemoglobin) was evaluated, MCHC (Mean Corpuscular Hemoglobin Concentration), RDW (Red Cell Distribution Width), HDI (Red Cell Dispersion Index), PWV (Platelet Volume) using ACTDiff Beckman colter automated analyzer. Everything was performed at the participating hospital following their internal procedures.

Total RNA extraction

5 mL for biometry and 10 mL for blood chemistry were extracted from peripheral blood in BD Vacutainer® tubes. For total RNA extraction, erythrocyte lysis was first performed using QIAamp RNA Blood Mini Producer kit (Quiagen, Cat. No. ID: 52304) according to the manufacturer's conditions. The total RNA obtained was quantified using the IMPLEN® NanoPhotometer P300 NP80 at 260/280 nm absorbance.

Reverse Transcription and Polymerase Chain Reaction (RT-PCR)

According to the manufacturer, 500 ng of total RNA was used for cDNA synthesis, Revert Aid First Strand cDNA Synthesis kit (Thermo Scientific K1622, Cat. No.ID:10387979) instructions, using the GeneAmp* PCR System 9700 thermal cycler. For endpoint PCR amplification, the MasterMix 2X kit (Promega, Cat. No. ID: M750) was used according to the manufacturer's instructions. For primers, the sequences were used for *ObRb*: Fw: 5'-GATAGAGAGGCCCAGGCATTTTTTA-3' and Rv:5'-ACACCACTCTCTCTCTCTCTCTCTTTTTTTGATTGA-3', for *AdipoR1*: Fw:5'-AATTCCTGAGCGCTTCTTCTTTCCT-3' and Rv: 5'-CATAGAAGAAGTGGACAAAGGCTGC-3', for *CYP19*: Fw:5'-CAAGGTTATTTTTTGAT GCATGG-3' and Rv:5'-AATCCTTGACAGACTTCTCAT-3', as constitutive gene 18S was used: Fw:5'-GTCTGTGATGATGCCCTTAGA TG-3' and Rv: 5'-AGCTTATGACCCGCACTTAC-3' [35-36]. They were taken to

incubation on the GeneAmp* PCR System 9700 thermal cycler with the following protocol: denaturation at 94 °C /1 min, hybridization at 60 °C /1 min, and extension at 72 °C /1 min for 35 cycles.

Electrophoresis

Products obtained from endpoint PCR were loaded onto a 2.0 % agarose gel (Sigma, Cat. No. ID: 1001134274), and electrophoresis (C. B. S. Scientific, MGU-203T-B) was run at 90 Volts for 40 min. This using 1X TAE run buffer (40mM Tris-Base (Sigma, Cat. ID No. ID 10708976001)), 40mM Acetic Acid (Sigma, Cat. ID No. ID A6283), 1mM EDTA (Sigma, Cat. ID No. ID E7889) with 0.01 % ethidium bromide (Sigma, Cat. ID No. ID: 1239458) as an intercalating agent to visualize the obtained amplicon bands. They were developed under UV light with the aid of the Photodocumentator (UV Transilluminator ANT Technology CUV 40A). Subsequently, the optical intensity of the obtained bands was quantified by densitometry and normalized to arbitrary units corresponding to the positive control of the constitutive 18S gene. Image J 1.52a software (Wayne Rasband) was used for image processing.

Statistical analysis

BMI data were analyzed using descriptive statistics for general qualitative and quantitative variables, using IBM SPSS Statistic 25 2017 statistical software. The correlation analysis of BMI expression concerning each *ObRb*, *AdipoR1*, and *CYP19* gene was analyzed through Pearson's correlation test for those with a normal distribution and Spearman for non-normal distribution data using IBM SPSS Statistic 25 2017 statistical software, considered a *p*-value of 0.05. GraphPad Prism 7 statistical software was used to generate the graphs.

Results

Determination of obesity and overweight according to BMI.

A population of n= 45 volunteers were observed with an average age of 60.7 ± 6.8 years and an average BMI of 27.9 ± 4.1 kg/m^2. They were classified according to BMI into three groups: a) Volunteers with average weight or normal weight, b) Volunteers with overweight, and c) Volunteers with obesity. We observed that 71.1 % of the population presented a BMI higher than 25 kg/m^2 (22.2 % with obesity and 48.9 % with overweight), while the remaining 28.9 % were within the normal BMI.

Hematological and biochemical characteristics.

According to Table 1, the data obtained from the blood biometry for the three groups average weight, overweight and obese, no significant differences were found. For the blood chemistry results, no significant differences

were found between groups. However, it was observed that 64 % of the participating volunteers showed an increase of more than 150 mg/dL in triglycerides,

Table 1. Hematologic and biochemical characteristics of the study population.

	Normal weight (n= 13)	Overweight (n= 22)	Obese (n=10)	p
Age (years)	60.84 ± 7.78	60.50 ± 7.80	60.4 ± 5.23	0.986
Weight (Kg)	58.00 (55.5-61.00)	64.85 (60.87-64.85)	76.50 (69.25-89.00)	0.000
Height (m)	1.56 ± 0.05	1.52 ± 0.06	1.52 ± 0.06	0.227
Leukocytes (10e3/µL)	6.18 ± 1.57	6.02 ± 1.58	6.83 ± 0.89	0.349
Neutrophils (%)	59.50 (55.75-65.60)	54.10 (46.45-61.25)	54.40 (52.27-58.35)	0.225
Lymphocytes (%)	28.13 ± 6.20	32.99 ± 10.69	32.61 ± 7.99	0.290
Monocytes (%)	5.32 ± 1.52	5.17 ± 1.34	5.49 ± 1.53	0.840
Eosinophils (%)	1.90 (1.45-3.80)	2.35 (1.57-3.95)	3.45 (2.87-4.45)	0.829
Basophils (%)	1.0 (0.62-1.87)	0.8 (0.75-1.75)	0.9 (0.67-1.52)	0.783
Erythrocytes (10e3/µL)	4.84 ± 0.26	4.79 ± 0.33	4.83 ± 0.28	0.878
Hgb (g/dL)	14.8 (41.1-14.8)	14.8 (14.27-15.67)	14.8 (13.77-15.67)	0.633
Hto (%)	47.08 ± 2.67	47.50 ± 3.60	45.61 ±4.32	0.377
MCV (fL)	96.6 (93.5-102.0)	99.25 (95.32-103.37)	95.36 (84.57-97.67)	0.031
HCM (pg)	30.0 (29.9-31.45)	31.0 (30.30-32.70)	30.60 (9.47-31.45)	0.333
MCHC (g/dL)	37.70 (30.05-32.70)	31.90 (30.27-33.05)	32.10 (30.92-33.44)	0.933
RDW (%)	13.0 (12.85-13.60)	13.10 (12.6 -13.65)	13.65 (12.97-14.32)	0.223
HDI (g/dL)	2.53 (2.34-2.75)	2.54 (2.42-2.77)	2.56 (2.37-2.73)	0.766
Platelets (10e3/µL)	261.23 ± 62.68	236.31 ± 47.61	258.90 ± 60.56	0.355
VMP (fL)	11.18 ± 1.19	11.51 ± 1.80	11.11 ± 1.96	0.766
Glucose (mg/dL)	95.4 (85.6-106.6)	99.7 (87.8-114.9)	95.90 (87.2-96.3)	0.565

	Normal weight (n= 13)	Overweight (n= 22)	Obese (n=10)	p
BUN (mg/dL)	13.0 (12.0-18.0)	28.8 (23.5-31.7)	18.0 (13.0-22.5)	0.078
Urea (mg/dL)	28.1 (26.3-38.8)	13.0 (11.0-15.0)	37.6 (27.4-48.05)	0.098
Creatinine (mg/dL)	0.79 ± 0.09	0.79 ± 0.11	0.89 ± 0.12	0.498
Uric acid (mg/dL)	4.78 ± 0.81	5.39 ± 0.79	5.70 ± 0.61	0.345
Cholesterol (mg/dL)	182.22 ± 19.44	196.08 ± 20.54	196.26 ± 14.43	0.547
Triglycerides (mg/dL)	170.9 (132.4-259.2)	158.2 (132.4-272.1)	205.8 (138.4-283.3)	0.976

Abbreviations: BMI (Body Mass Index), Hgb (Hemoglobin), Hto (Hematocrit), MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Hemoglobin), MCHC (Mean Corpuscular Hemoglobin Concentration), RDW (Red Cell Distribution Width), HDI (Red Cell Dispersion Index), PWV (Platelet Volume). * Data out of range of the upper limit allowed.

Overexpression of ObRb and AdipoR1 genes in overweight and obesity

Endpoint RT-PCR detected *ObRb, AdipoR1*, and *CY19* genes. Fragments of each of them can be seen in Figure 1, which allowed us to detect differences in the genes' expression among the participating volunteers.

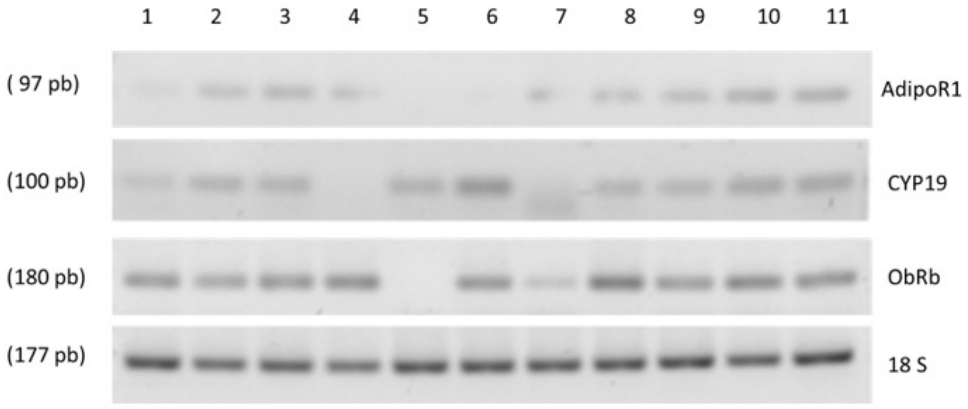

Figure 1. ObRb, AdipoR1, and CYP19 expression levels in postmenopausal women. Notes: The image of ObRb, AdipoR1, and CYP19 expression levels shows the bands obtained from the RT-PCR reaction, including the 18S positive control.

The optical intensity of the obtained bands normalized to arbitrary units concerning the positive control of the constitutive *18S* gene was quantified (Figure 2).

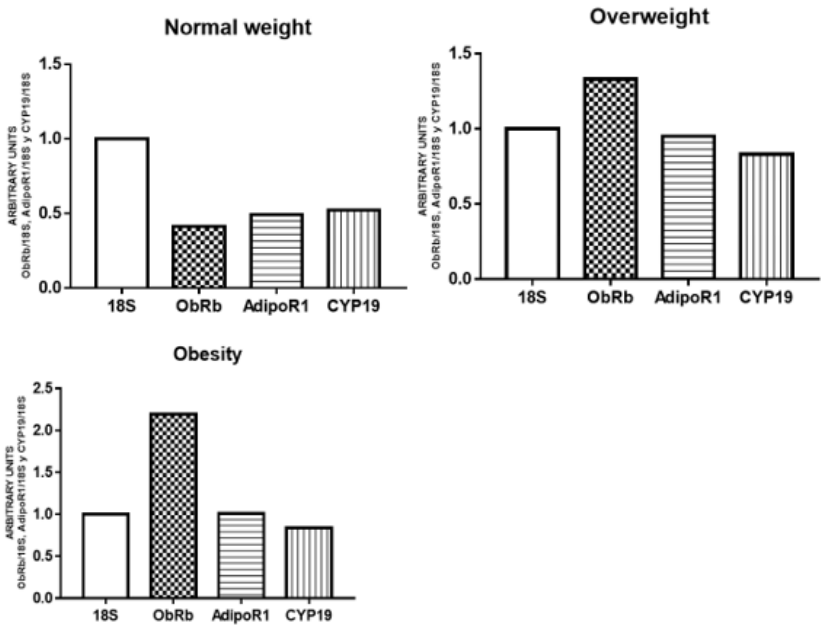

Figure 2. Effect of overweight and obesity on ObRb overexpression. Notes: Representative image of the effect of overweight and obesity on ObRb and AdipoR1 overexpression. The optical intensity of the bands obtained by RT-PCR was quantified and normalized to arbitrary units concerning the positive control of the constitutive 18S gene.

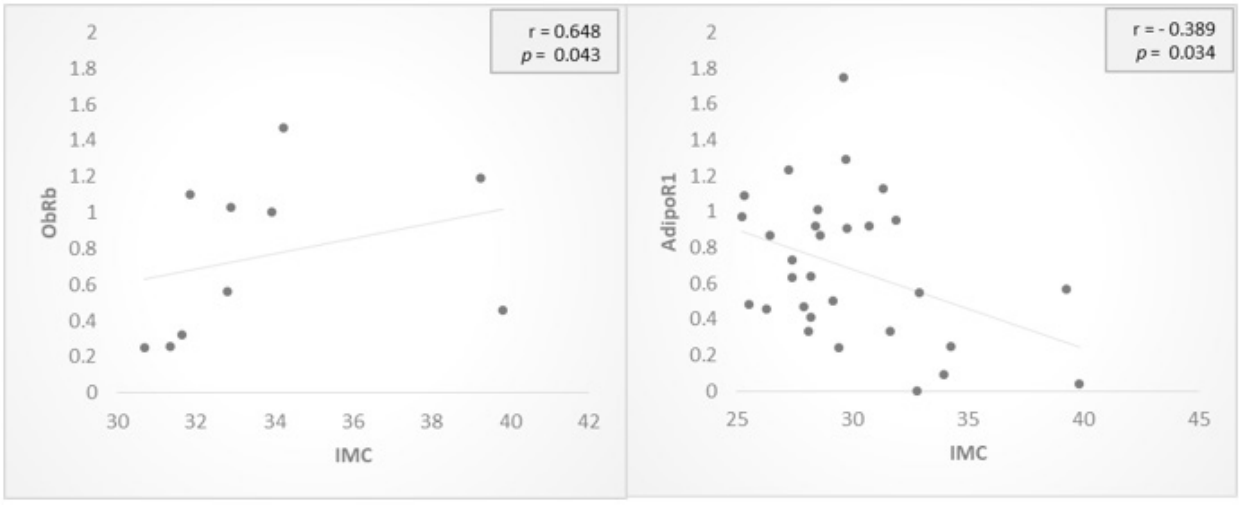

Figure 3. Correlation of ObRb, AdipoR1 gene expression for BMI. Notes: Scatter plot of the correlation of ObRb gene expression with BMI greater than 30 kg/m2 on the right (r=0.648, p=0.043) and for AdipoR1 gene with BMI greater than 25 kg/m2 (r= -0.389, p=0.034) on the left.

Table 2 shows the evaluation of the correlation of *ObRb, AdipoR1*, and *CY19* gene expression for BMI, considering the classification of the 3 study groups (average weight, overweight and obese). Significant differences were obtained for the *ObRb* gene with BMI higher than 30 kg/m^2 (p=0.043) and for the *AdipoR1* gene with BMI higher than 25 kg/m^2 (p=0.034), suggesting an association of the expression of these genes with increased BMI (Figure 2 and 3). We found no significant differences in control for the gene coding for the aromatase enzyme (*CYP19*).

Table 2. Correlation of ObRb, AdipoR1, and CYP19 gene expression coding for aromatase enzyme.

Gen/IMC	< 25 Kg/m2		> 25 Kg/m2		> 30 Kg/m2	
	r	*p*	r	*p*	r	*p*
ObRb	0.217	0.576	0.165	0.382	0.648*	0.043
AdipoR1	0.444	0.231	-0.389**	0.034	-0.464	0.177
CYP19	0.343	0.366	0.168	0.376	-0.115	0.751
* Moderate correlation * * Negative moderate correlation						
Notes: BMI less than 25 Kg/m2 (average weight), greater than 25 Kg/m2 (overweight), and greater than 30 Kg/m2 (obesity), respectively.						

Discussion

Our study obtained from the analysis concerning BMI showed a prevalence of up to 71.1 % of obesity (22.2 %) and overweight (48.9 %). Similarly, in the 2018 Health and Nutrition Survey (ENSANUT), a prevalence in women worldwide in Mexico was estimated at 78.1 % when BMI was higher than 25 kg/m^2 [3].

However, several studies have suggested using BMI as an anthropometric indicator to determine obesity and metabolic risk factors. Furthermore, they should also consider waist circumference values since it is necessary to distinguish between body fat and fat-free mass[37-39].

In this sense, the guidelines on Prevention, Diagnosis, and Treatment of Overweight and Obesity suggest the performance of clinical studies during the evaluation of patients with overweight and obesity, including blood biometry and other parameters [40]. It is important to emphasize that the evaluation of these clinical studies also allows the early recognition of some metabolic or cardiovascular diseases as recommended by the *Canadian Clinical Practice Guidelines on the Management and Prevention of Obesity in Adults and Children 2006* [41]. Notably,

we did not observe significant differences between the study groups.

Additionally, during the determination of some parameters, as in the case of triglycerides, 64 % of the studied population obtained an increase higher than 150 mg/dL, which is a normal range considered as healthy, which could indicate a possible association of increased BMI with high triglyceride levels as shown by Calleja and Sanchez (2012) [42]. It is essential to consider that the age of this study group was above 55 years of age, and it is suggested that they were close to the postmenopausal stage. Likewise, Escobedo *et al.* (2014) noticed that the older the age, the higher the prevalence of presenting increased triglycerides, and that the presence of the postmenopausal stage could be directly related to BMI [28, 43-46].

On the other hand, one of the causes of BMI variations is due to genetic differences, in this sense Tuomo Rankinen *et al.* (2005) presented the map of genes related to human with obesity, reporting an association between DNA sequence variation in specific genes such as *ObRb, AdipoR1*, and *CYP19* and phenotypes. However, these differ between populations [20].

Our analysis of the long leptin receptor expression known as *ObRb* showed a moderate correlation of expression in women with obesity (r=0.648, p=0.043). Several authors have studied the expression of this gene in various populations and have reported that it plays a fundamental role in the pathophysiology of obesity by favoring an increase in % body weight [47, 48].

In the same way, we found a moderate negative correlation of the *AdipoR1* gene with overweight or obesity (r= -0.389, p=0.034), coinciding with the finding of Rasmussen *et al.* (2012), where it decreased in the presence of obesity but increased in the presence of overweight [31].

Indeed, we could not determine an association with the *CYP19* gene, possibly due to some variations between individuals. However, we suggest studying the presence of genetic polymorphisms that provide more information about the association of this gene with BMI [33].

Conclusions

The present study demonstrated that.

1. There is a moderate correlation of *ObRb* gene expression for patients with BMI greater than 30 Kg/m^2 (r=0.648, p=0.043) and moderate negative correlation with the *AdipoR1* gene for patients with BMI greater than 25 Kg/m^2 (r= -0.389, p=0.034) in Mexican women from the State of Mexico and older than 55 years of age who are healthy. However, it is essential to ensure the data replication and extrapolate it to the entire Mexican female population, having more varia-

bles that can influence the diagnosis of this pathology and can be used as predisposing factors.

2. The increase of more than 150 mg/dL of triglycerides in our study population alludes to increased lipoproteins and, therefore, the possible presence of dyslipidemia associated with obesity is possibly caused by physical inactivity inadequate nutrition. However, it is essential to corroborate the behavior of this parameter and others such as cholesterol in different populations to confirm the diagnosis.

3. We suggest the importance of studying genetic polymorphisms or SNPs in the genes involved with variations in BMI and determining the circulating blood levels of certain adipokines such as leptin and adiponectin provide more information about the association with this pathology and the different phenotypes.

4. We also suggest the importance of promoting physical activity and providing help on balanced diets to maintain a BMI below 25 kg/m^2, thus mitigating the risk of developing obesity and developing metabolic and cardiovascular diseases.

Conflict of interests: There is no conflict of interest.

Acknowledgments: We gratefully acknowledge financial support from SEIA UAEM 6247/2020.

References

1. Malo SM, Castillo MN, Pajita DD. Obesity in the world. *An la Fac Med*. 2017;78(2):67.
2. Wang Y, Beydoun MA, Liang L, Caballero B, Kumanyika SK. Will all Americans become overweight or obese? Estimating the progression and cost of the US obesity epidemic. Obesity. 2008;16(10):2323–30.
3. Encuesta Nacional de Salud y Nutrición 2018. Instituto Nacional de Estadística y Geografía, Instituto Nacional de Salud Pública, Secretaría de Salud;1:47.
4. Guendelman S, Ritterman-Weintraub ML, Fernald LCH, Kaufer-Horwitz M. A population-based comparison of weight and weight perceptions among overweight and obese Mexican and Mexican-American men. Salud Publica Mex. 2013;55(1 SUPPL.4):451–8.
5. Herrera B, Lindgren C. The genetics of obesity. Curr Diab Rep. 2010;10(6):498–505.
6. Ristow M, Müller-Wieland D, Pfeiffer A, Krone W, Kahn CR. Obesity Associated with a Mutation in a Genetic Regulator of Adipocyte Differentiation. New England Journal of Medicine. 2002;339(14):953–9.
7. Obesidad y sobrepeso; 2020. Organización Mundial de la Salud.
8. Wyatt SB, Winters KP, Dubbert PM. Overweight and obesity: Prevalence, consequences, and causes of a growing public health problem. Am J Med Sci. 2006;331(4):166–74.
9. Crake RLI. Exploring Molecular Links between Obesity and Breast Cancer. 2015.
10. D'Angelo CS, Varela MC, De Castro CIE, et al. Chromosomal microarray analysis in the genetic evaluation of 279 patients with syndromic obesity. Mol Cytogenet. 2018;11(1):1–18.
11. Nickel A, Blücher C, Kadri O Al, et al. Adipocytes induce distinct gene expression profiles in mammary tumor cells and enhance inflammatory signaling in invasive breast cancer cells. Sci Rep. 2018;8(1):9482.

12. Pavón De Paz I, Alameda Hernando C, Olivar Roldán J. Obesity and menopause. Nutr Hosp Organo Of la Soc española Nutr Parenter y Enter. 2006;21(6):633–7.

13. Garaulet M, Pérez-Llamas F, Zamora S, Javier Tébar F. Comparative study of the type of obesity in pre- and postmenopausal women: Relationship with fat cell data, fatty acid composition and endocrine, metabolic, nutritional and psychological variables. Med Clin. 2002;118(8):281–6.

14. Moleres A., Martinez JA., Marti A. Genetics of obesity. Aust Fam Physician. 2017;46(7):456–9.

15. Scuteri A, Sanna S, Chen WM, et al. Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. PLoS Genet. 2007;3(7):1200–10.

16. Singh RK, Kumar P, Mahalingam K. Molecular genetics of human obesity: A comprehensive review. Comptes Rendus - Biol. 2017;340(2):87–108.

17. Thaker VV. Genetic and Epigenetic Causes of Obesity. Adolesc Med State Art Rev. 2017;28(2):379–405.

18. González JE. Genes and obesity: a cause and effect relationship. Endocrinol y Nutr. 2011;58(9):492–6.

19. Martos GÁ, Serra JC, Pérez JL, Argente J. Aspectos genéticos de la obesidad. Rev Esp Endocrinol Pediatr. 2017;8:21–32.

20. Rankinen T, Zuberi A, Chagnon YC, et al. The human obesity gene map: The 2005 update. Obesity. 2005;14(4):529–644.

21. García TD, Castellanos MF, Cedeño MR, Benet RM, Ramírez AI. Adipose tissue as an endocrine glans. Pathophysiological implications. Finlay. 2014;1(2):131–6.

22. Garcés MF, Gomes B, Stekman H, Hernández C, López, Soto I. Polimorfismos G2548A del gen de leptina y Gln223Arg del gen repector de leptina en pre-púberes con riesgo cardiometabolico. Arch Venez Pueric Pediatr. 2016;79(1):54–61.

23. Geriki S, Bitla AR, SrinivasaRao PVLN, et al. Association of single nucleotide polymorphisms of adiponectin and leptin genes with breast cancer. Mol Biol Rep. 2019;46(6):6287–97.

24. Fangyi G. Leptin and leptin receptor genes in relation to premenopausal breast cancer incidence and grade in Caucasian women. Breast Cancer Res Treat. 2013;23(1):1–7.

25. Mahmoudi R, Noori AB, Nazer MMA, Fararouei M, Nikseresht M. Polymorphisms of Leptin (-2548 G/A) and Leptin Receptor (Q223R) Genes in Iranian Women with Breast Cancer. Int J Genomics. 2015;2015.

26. Daghestani M, Purohit R, Daghestani M, Daghistani M, Warsy A. Molecular dynamic (MD) studies on Gln233Arg (rs1137101) polymorphism of leptin receptor gene and associated variations in the anthropometric and metabolic profiles of Saudi women. PLoS One. 2019;14(2):1–15.

27. Karim S, Merdad A, Schulten HJ, et al. Low expression of leptin and its association with breast cancer: A transcriptomic study. Oncol Rep. 2016;36(1):43–8.

28. Rodríguez A, Echandía C, Sánchez A, et al. Complexity of the expression of genes associated with obesity in human adipose tissue. Rev Med. 2018;26(1):2018.

29. Gómez RP, Alarcón SA, Rodríguez WF, Díaz GE. Adiponectin as therapeutic targe. Med Interna Mex. 2017;33(6):770–7.

30. Martinez JE, Suárez JA, Martínez M, et al. Role of adiponectine on obesity and diabetes type 2. Med Interna Mex. 2019;35(3):389–96.

31. Rasmussen MS, Lihn AS, Pedersen SB, Bruun JM, Rasmussen M, Richelsen B. Adiponectin receptors in human adipose tissue: Effects of obesity, weight loss, and fat depots. Obesity. 2006;14(1):28–35.

32. Chen J, Shen S, Tan Y, et al. The correlation of aromatase activity and obesity in women with or without polycystic ovary syndrome. J Ovarian Res. 2015;8(1):4–9.

33. Gennari L, Masi L, Merlotti D, et al. A polymorphic CYP19 TTTA repeat influences aromatase activity and estrogen levels in elderly men: Effects on bone metabolism. J Clin Endocrinol Metab. 2004;89(6):2803–10.

34. Declaraciòn de Helsinki de la AMM – Principios Éticos para las Investigaciones Mèdicas en seres humanos, 2013. Asociaciòn Mèdica Mundial.

35. Linares RL, Santillán JGB, Ortiz MR, Romero CG, Sandoval-Cabrera A. Modulation of the leptin receptors expression in breast cancer cell lines exposed to leptin and tamoxifen. Sci Rep. 2019;9(1):1–9.

36. Mociño MDR, Santillán JGB, Dozal DSD, et al. Expression of AdipoR1 and AdipoR2 Receptors as Leptin-Breast Cancer Regulation Mechanisms. Dis Markers. 2017;2017:1–11.

37. Mirele DO, Fagundes R, Moreira E, de Moraes Trindade E, de Carvalho T. Relación de indicadores antropométricos con factores de riesgo para enfermedad cardiovascular. Arq Bras Cardiol. 2010;94(4):462–9.

38. Domínguez TR, Quiroz IV, Bernabé ABS, Goytia LS, Valle JFM, Isela PR. Las medidas antropométricas como indicadores predictivos de riesgo metabólico en una población mexicana. Nutr Hosp. 2016;31(4):6–14.

39. Cedeño RM, Castellanos MBG-RMG, Mass LS, Mora CH, Parada JA. Anthropometric Indicators to Determine the Obesity and its Relations with the Cardiometabolic Risk. Rev Finlay, 2015;5(1):11.

40. Guia para la prevencion, diagnostico y tratamiento del sobrepeso y obesidad. 2012; IMSS.

41. Lau D, Douketis D, Morrison K, Hramiak I, Sharma A, Ur E. Canadian Guidelines for obesity. Can Med Assoc J. 2007;176(8).

42. Calleja HG, Sanchez DL. Relación entre circunferencia abdominal e índice de masa corporal con los niveles de colesterol total y trigliceridos en los pacientes que acuden la centro de saul rural disperso Santa Maria, Mexico. Universidad Autonoma del Estado de México. 2012.

43. Pavía AA, Aguilar CS. Mexican guidelines in the diagnosis and treatment of dyslipidemias and atherosclerosis. Statement of the Mexican Society of Cardiology. Med Interna Mex. 2020;36(3):390–413.

44. Fuentes GO, Mata AH. Frecuencia de hipertrigliceridemias en población mexicana ambulatoria. Rev Latinoam Patol Clínica y Med Lab. 2013;60(2):110–5.

45. Carranza LM. Triglycerides and cardiovascular risk. Med Int Méx. 2017;33(4):511–4.

46. Escobedo JP, De Jesús P, Schargrodsky H, Champagne B. Prevalencia de dislipidemias en la ciudad de México y su asociación con otros factores de riesgo cardiovascular. Gac Med Mex. 2014;150:1–9.

47. Collares RVA, Salgado W, Da Cunha Tirapelli DP, Dos Santos JS. The expression of LEP, LEPR, IGF1 and IL10 in obesity and the relationship with microRNAs. PLoS One. 2014;9(4):1–6.

48. Yiannakouris N, Yannakoulia M, Melistas L, Chan JL, Klimis-Zacas D, Mantzoros CS. The Q223R polymorphism of the leptin receptor gene is significantly associated with obesity and predicts a small percentage of body weight and body composition variability. J Clin Endocrinol Metab. 2001;86(9):4434–9.