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

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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/m². 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.

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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.

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**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. 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.

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). 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$^2$.

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.

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

\[
\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}
\]
To classify the study population, the recommended criteria by the WHO were used: average weight (BMI < 25 kg/m²), overweight (BMI ≥ 25 kg/m²), and obesity (BMI ≥ 30 kg/m²) 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'-GATAGAGAGCCAGATTTTTTA-3' and Rv:5'-ACAC-CACTCTCTCTCTCTCTCTCTCTCA-3', for AdipoR1: Fw:5'-AATTCCTGAGCGCTTCTTCT-3' and Rv: 5'-CATAGAAGAAGAGGGCCTGC-3', for CYP19: Fw:5'-CAAGGTTATTTTGACTGCAT-3' and Rv:5'-CAAGGTTATTTTGACTGCAT-3', as constitutive gene 18S was used: Fw:5'-GTCTGTGATGATGCCCTTAGATGTA TG-3' and Rv: 5'-AGCTTATGACC-CGCACCTTAC-3'. 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/m². 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/m² (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.

<table>
<thead>
<tr>
<th></th>
<th>Normal weight (n=13)</th>
<th>Overweight (n=22)</th>
<th>Obese (n=10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.84 ± 7.78</td>
<td>60.50 ± 7.80</td>
<td>60.4 ± 5.23</td>
<td>0.986</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>58.00 (55.5-61.00)</td>
<td>64.85 (60.87-64.85)</td>
<td>76.50 (69.25-89.00)</td>
<td>0.000</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.56 ± 0.05</td>
<td>1.52 ± 0.06</td>
<td>1.52 ± 0.06</td>
<td>0.227</td>
</tr>
<tr>
<td>Leukocytes (10×10^3/µL)</td>
<td>6.18 ± 1.57</td>
<td>6.02 ± 1.58</td>
<td>6.83 ± 0.89</td>
<td>0.349</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>59.50 (55.75-65.60)</td>
<td>54.10 (46.45-61.25)</td>
<td>54.40 (52.27-58.35)</td>
<td>0.225</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>28.13 ± 6.20</td>
<td>32.99 ± 10.69</td>
<td>32.61 ± 7.99</td>
<td>0.290</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>5.32 ± 1.52</td>
<td>5.17 ± 1.34</td>
<td>5.49 ± 1.53</td>
<td>0.840</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>1.90 (1.45-3.80)</td>
<td>2.35 (1.57-3.95)</td>
<td>3.45 (2.87-4.45)</td>
<td>0.829</td>
</tr>
<tr>
<td>Basophils (%)</td>
<td>1.0 (0.62-1.87)</td>
<td>0.8 (0.75-1.75)</td>
<td>0.9 (0.67-1.52)</td>
<td>0.783</td>
</tr>
<tr>
<td>Erythrocytes (10×10^3/µL)</td>
<td>4.84 ± 0.26</td>
<td>4.79 ± 0.33</td>
<td>4.83 ± 0.28</td>
<td>0.878</td>
</tr>
<tr>
<td>Hgb (g/dL)</td>
<td>14.8 (41.1-14.8)</td>
<td>14.8 (14.27-15.67)</td>
<td>14.8 (13.77-15.67)</td>
<td>0.633</td>
</tr>
<tr>
<td>Hto (%)</td>
<td>47.08 ± 2.67</td>
<td>47.50 ± 3.60</td>
<td>45.61 ±4.32</td>
<td>0.377</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>96.6 (93.5-102.0)</td>
<td>99.25 (95.32-103.37)</td>
<td>95.36 (84.57-97.67)</td>
<td>0.031</td>
</tr>
<tr>
<td>HCM (pg)</td>
<td>30.0 (29.9-31.45)</td>
<td>31.0 (30.30-32.70)</td>
<td>30.60 (9.47-31.45)</td>
<td>0.333</td>
</tr>
<tr>
<td>MCHC (g/dL)</td>
<td>37.70 (30.05-32.70)</td>
<td>31.90 (30.27-33.05)</td>
<td>32.10 (30.92-33.44)</td>
<td>0.933</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>13.0 (12.85-13.60)</td>
<td>13.10 (12.6 -13.65)</td>
<td>13.65 (12.97-14.32)</td>
<td>0.223</td>
</tr>
<tr>
<td>HDI (g/dL)</td>
<td>2.53 (2.34-2.75)</td>
<td>2.54 (2.42-2.77)</td>
<td>2.56 (2.37-2.73)</td>
<td>0.766</td>
</tr>
<tr>
<td>Platelets (10×10^3/µL)</td>
<td>261.23 ± 62.68</td>
<td>236.31 ± 47.61</td>
<td>258.90 ± 60.56</td>
<td>0.355</td>
</tr>
<tr>
<td>VMP (fL)</td>
<td>11.18 ± 1.19</td>
<td>11.51 ± 1.80</td>
<td>11.11 ± 1.96</td>
<td>0.766</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>95.4 (85.6-106.6)</td>
<td>99.7 (87.8-114.9)</td>
<td>95.90 (87.2-96.3)</td>
<td>0.565</td>
</tr>
</tbody>
</table>
Overexpression of ObRb and AdipoR1 genes in overweight and obesity

Endpoint RT-PCR detected ObRb, AdipoR1, and CYP19 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.

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

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.

**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.
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Table 2 shows the evaluation of the correlation of ObRb, AdipoR1, and CYP19 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/m² (p=0.043) and for the AdipoR1 gene with BMI higher than 25 kg/m² (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>
<thead>
<tr>
<th>Gen/IMC</th>
<th>&lt; 25 Kg/m²</th>
<th>&gt; 25 Kg/m²</th>
<th>&gt; 30 Kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
</tr>
<tr>
<td>ObRb</td>
<td>0.217</td>
<td>0.576</td>
<td>0.165</td>
</tr>
<tr>
<td>AdipoR1</td>
<td>0.444</td>
<td>0.231</td>
<td>-0.389**</td>
</tr>
<tr>
<td>CYP19</td>
<td>0.343</td>
<td>0.366</td>
<td>0.168</td>
</tr>
</tbody>
</table>

* 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/m².

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.

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. 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. 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 BMI28, 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 populations20.

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 weight47, 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 overweight31.

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 BMI33.

Conclusions

The present study demonstrated that.

1. There is a moderate correlation of ObRb gene expression for patients with BMI greater than 30 Kg/m² (r=0.648, p=0.043) and moderate negative correlation with the AdipoR1 gene for patients with BMI greater than 25 Kg/m² (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/m², thus mitigating the risk of developing obesity and developing metabolic and cardiovascular diseases.

**Conflict of interests:** There is no conflict of interest.

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