Research Article
The Association between the Levels of Phosphodiesterase 9, Insulin-like peptide 5 and Obesity in Women
Zuhair Assi Hussein1*, Maysaa Jalal Majeed1, Lubna Amer Al-Anbari2, Suzan Adil Rashid Al-Naqeeb3

1 University of Baghdad, College of Medicine, Baghdad, Iraq
2 High Institute for Infertility Diagnosis and ARTS, Al-Nahrain University, Baghdad, Iraq
3 Northern Technical University, Kirkuk, Iraq

1* Corresponding author's email: zuhairkirkuk2015@gmail.com

ABSTRACT

Background: The obesity epidemic is affecting worldwide health, increasing the risk of cardiovascular diseases such as hypertension, diabetes, dyslipidemia, and nonalcoholic fatty liver disease. This gave an impetus to study the new variables Insulin-like peptide 5, Phosphodiesterase 9, and their relationship as a cause or effect factors.

Objective: To validate any associations between Phosphodiesterase 9 (PDE9) and Insulin-like peptide 5 (INSL5), specific factors and obesity, and to explore how they might integrate with other established agents to combat obesity and improve metabolism.

Subjects and Methods: The study was based analytical cross-sectional research was conducted from (February 2022) to (August 2022). The study based on apparently healthy women (primary analyses were made, their blood sugar and lipid profile with the normal reference range) 50 women with age range (20 – 40) years. Fasting blood samples were collected from all the participants in the study, (5 ml) was poured in plane tubes and sera were separated by centrifuging the samples for 10 minutes at 3000rpm for the biochemical and hormonal investigations, therefore they were divided into two group: -first group: consisted of twenty-five obese women without previously diagnosed diseases (BMI > 30 kg/m2). second group: consisted of twenty-five women with normal BMI (BMI= 24.9-18.5 kg/m2).

Results: Serum insulin-like peptide 5 showed significant increase in obese women without previously diagnosed diseases (16.31±3.88 μIU/ml), in comparison with women with normal BMI (8.11± 1.52ng/ml). Serum PDE-9A significantly ((P≤ 0.05) decrease in obese women (6.77±1.95ng/ml), in comparison with women with normal BMI (8.11± 1.52ng/ml).

Conclusions: Insulin-like peptide 5 (INSL5) could play a role in promoting insulin resistance (IR), Phosphodiesterase 9 (PDE9) is a regulator of energy. Phosphodiesterase 9 (PDE9) inhibition is associated with increase the occurrence of insulin resistance.

Introduction
Obesity is a phrase that carries a lot of weight due to differing cultural conventions and stigmas concerning body size and form. The World Health Organization (WHO) defines "overweight" as a BMI 25 or higher, and "obese" as a BMI 30 or higher (1) abnormal or excessive fat buildup in the body that may be harmful to health, insulin triggers fat storage in the body (2,3). This important hormone, which also regulates blood sugar levels and helps to absorb glucose, also controls the fat building process. Insulin promotes the conversion of fatty acids into fat molecules, which are then stored in the body as fat droplets.

Hepatic or central nervous system insulin resistance may occur first, but we lack the means to detect it; then follows hyperinsulinemia, followed by obesity, and lastly peripheral insulin resistance, in a vicious cycle (4-6).

Insulin-like peptide (INSL) 5 is a member of the relaxin/insulin family, which also includes insulin, IGF (insulin-like growth factor) 1 and 2 (7,8), relaxin 1 and 2, and Insulin-like peptide-7 (8,9), and was recently discovered in colonic and brain tissue. INSL5's function is unknown, despite the fact that other members of the relaxin/insulin group have roles in glucose metabolism, reproduction physiology, and connecting tissue remodeling (10).

https://doi.org/10.47723/6btq4431

https://doi.org/10.47723/6btq4431
Subjects and Methods
The study included the age range (20 – 40) years. Their selection was made to serve the aim of the study therefore they were divided into two groups:
• First Group: consisted of twenty-five obese women without previously diagnosed diseases (BMI≥ 30kg/m²).
• second Group: consisted of twenty-five women with normal BMI (BMI= 24.9–18.5 kg/m²).
All women with metabolic or endocrinology disorders were excluded from this study, including Diabetes mellitus, Hypertension, Liver disease, Chronic renal disease, Premature ovarian failure.

Using the Magnum-800 Chemiluminescence Immunoassay (CLIA) System, insulin analysis was performed on fasting serum samples. The serum concentrations of INSL5 and PDE-9 were determined using an ELISA instrument. Using the BK-500 Auto Chemistry Analyzer, the serum levels of glucose, and lipid profile level were measured in accordance with the manufacturer's instructions. SPSS-22 program was dependent in the statistical analyses of the study's data, student’s t-test was used in the determination of the significant level between the two groups. While the Pearsons correlation was dependent in the association determination between two parameters. Homeostasis model assessment of insulin resistance (HOMA-IR) calculates the IR by dividing the product of fasting plasma glucose (mmol/l) x fasting plasma insulin (µIU/ml) by a constant, i.e 22.5 as shown in the following formula. HOMA-IR=Fasting plasma glucose (mmol/l) x Fasting plasma insulin (µU/mL)/22.5. A HOMA-IR value equal to or more than 2.5 was regarded as insulin resistant.

All research ethical Committee of the College of Medicine, University of Baghdad approved the study.

Table (1): General demographic characteristics of the study's population

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Groups</th>
<th>No</th>
<th>Mean ±SD</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>women with normal BMI (A)</td>
<td>25</td>
<td>24.36 ± 4.06</td>
<td>0.14</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>Obese women (B)</td>
<td>25</td>
<td>27.04 ± 5.86</td>
<td>(n.s)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>Obese women (B)</td>
<td>25</td>
<td>34.70 ± 3.24</td>
<td>(s)</td>
</tr>
<tr>
<td></td>
<td>women with normal BMI (A)</td>
<td>25</td>
<td>21.20 ± 2.26</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Obese women (B)</td>
<td>25</td>
<td>64.08 ± 4.80</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Table (2): mean ± SD of Serum insulin, SFG, HOMA-IR and lipid profile for obese women with normal BMI

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Groups</th>
<th>No</th>
<th>Mean ±SD</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin(µIU/ml)</td>
<td>women with normal BMI (A)</td>
<td>25</td>
<td>11.17±3.88</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Obese women (B)</td>
<td>25</td>
<td>16.31±3.88</td>
<td>(n.s)</td>
</tr>
<tr>
<td>S.FG(mmol/l)</td>
<td>BMI (A)</td>
<td>25</td>
<td>4.85±0.76</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Obese women (B)</td>
<td>25</td>
<td>5.92±0.10</td>
<td>(s)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>BMI (A)</td>
<td>25</td>
<td>2.36±0.78</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Obese women (B)</td>
<td>25</td>
<td>3.98±0.95</td>
<td>(s)</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>women with normal BMI (A)</td>
<td>25</td>
<td>153.76±22.82</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Obese women (B)</td>
<td>25</td>
<td>173.30±33.93</td>
<td>(n.s)</td>
</tr>
<tr>
<td>STG ( mg/dl )</td>
<td>BMI (A)</td>
<td>25</td>
<td>86.24±28.46</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Obese women (B)</td>
<td>25</td>
<td>117.14±31.19</td>
<td>(s)</td>
</tr>
<tr>
<td>S.HDL (mg/dl)</td>
<td>BMI (A)</td>
<td>25</td>
<td>38.64±4.150</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Obese women (B)</td>
<td>25</td>
<td>29.76±2.75</td>
<td>(s)</td>
</tr>
<tr>
<td>S.LDL (mg/dl)</td>
<td>BMI (A)</td>
<td>25</td>
<td>106.17±20.13</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>Obese women (B)</td>
<td>25</td>
<td>120.11±31.82</td>
<td>(n.s)</td>
</tr>
<tr>
<td>S.VLDL (mg/dl)</td>
<td>BMI (A)</td>
<td>25</td>
<td>17.25±3.69</td>
<td>0.04</td>
</tr>
</tbody>
</table>

All participants in this research were informed about the idea of the research and the reason for conducting it, a signed consent was obtained from each person on whom the study was performed.

Current study is analytical cross- section depending on the outcome of obesity.
Student t-test analyses was dependent, mean ± SD, (s) = Significant P≤0.05, (n.s) = Non-Significant P>0.05.

The measures of insulin resistance, using HOMA-IR equation the Mean ±SD for Obese women, serum insulin is (16.31±3.88) µIU/ml, and fasting glucose (5.92± 0.10) mmol/l, while the Mean ±SD for women with normal BMI serum insulin is (11.17±3.88) µIU/ml, and fasting glucose (4.85± 0.76) mmol/l demonstrate a notable statistically significant rise in obese women when compared to women with normal BMI. However, it is important to highlight that these values remain within the normal reference range. Additionally, it is noteworthy to consider the association between obesity and issues related to abnormalities in lipid profile shown in table (2).

The mean ±SD of the results serum PDE9A of women with normal BMI show significant increase in its level in comparison with obese women, on the contrary serum INSL5 of obese show significant increase in its level in comparison with women with normal BMI shown in table (3).

Table (3): mean ± SD of serum PDE9A and INSL5 for obese women compared with women normal BMI

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Groups</th>
<th>No</th>
<th>Mean ±SD</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. PDE-9A (ng/ml)</td>
<td>women with normal BMI (A)</td>
<td>25</td>
<td>8.11± 1.52</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>Obese women (B)</td>
<td>25</td>
<td>6.77±1.95</td>
<td>(s)</td>
</tr>
<tr>
<td>S. INSL5 (ng/ml)</td>
<td>women with normal BMI (A)</td>
<td>25</td>
<td>72.61±17.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obese women (B)</td>
<td>25</td>
<td>3</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Student t-test analyses was dependent, mean ± SD, (s) = Significant P≤0.05 (n.s) = Non-Significant P>0.05,

HOMA-IR of obese women showed significant positive correlation with INSL5 (r = 0.43, P= ≤ 0.05), while it showed a negative significant with serum PDE9A (r = -0.87, P=≤0.05).

Discussion

It was noticed an increase in the insulin level in obese women when compared to normal weight, which indicates and gives an indication of the presence of insulin resistance while their INSL5 level increased, which point to the connection with insulin resistance. Although various investigations have shown that INSL5 has an effect on the metabolism of glucose and lipids, the physiological role of INSL5 in the individual's metabolic system is unclear. Controlling mouse dietary intake, body weight, and glucose levels (16-18). However, INSL5 reduced the number of beta cells in the pancreas and insulin production, resulting in a significant increase in blood glucose levels (19,20). INSL5 has been reported to co-store with glucagon-like peptide-1, or GLP-1 and peptides YY, and it has been proven in vitro and in vivo to activate insulin and GLP-1 (21, 22). INSL5 did not correlate with the levels of total cholesterol, triglycerides, HDL, or LDL in the research, as it was presented in table2, which is consistent with some but not all earlier investigations found that raising INSL5 had no effect on food intake, body weight, or glucose management (18).

Another study reported that INSL5 enhances glucose-stimulated insulin secretion, both in vivo and in vitro (16). A more study suggested that INSL5 is an orexigenic gut hormone that is upregulated after fasting and calorie restriction from this Therefore, it is expected that the liver level will change, but usually these processes are subject to insulin regulation, and since women are classified as healthy people, it did not find a clear change in the lipid level (17).

A study discovered that mice lacking PDE9 acquire less weight than wild-type mice when exposed to a high-fat diet due to an increase in global energy expenditure. This modest rise in the consumption of energy at any given time led to a significant decrease in body weight and fat mass over the duration of the 16-week study, during which the rodents were fed a high-fat diet, consistent with the study's findings (23).

The possibility suggests that significant changes in the adipose tissue of these PDE9 knockout mice contributed to higher energy expenditure; the adipose tissue of the PDE9 mice elevated respiratory capacity (i.e., increased metabolism); and the researchers observed an increase in gene expression related to thermal activity in both white and brown adipose tissue. Improvements in the ability to control blood sugar levels have been linked to a decrease in body mass. In addition, the livers of PDE9 mice were resistant to the high-fat diet-induced lipid accumulation and liver injury. Inhibition of phosphodiesterase 9A (PDE9-I) prevents severe diet-induced obesity and metabolic cardiometabolic syndrome (CMS) in both male and female.
ovariectomized mice, with or without superimposed modest cardiac stress load (24). Phosphodiesterase 9A PDE9-I inhibition reduces total body, inguinal, hepatic, and cardiac fat, enhances the activity of mitochondria in brown and white fat, and improves cardiometabolic syndrome without substantially affecting activity or food intake. PDE9 was discovered in mitochondria, and blocking it boosted PPAR-dependent lipolysis while simultaneously enhancing the respiration of mitochondria in both fatty tissue and myocytes in vitro (25). PPAR activation was required to achieve PDE9-I's lipolytic, antiobesity, and metabolic benefits. None of these PDE9-I-induced modifications were detected in obese CMS patients; despite the fact that PDE9 inhibitors offer a lot of benefits and good therapeutic outcomes, less investigations on them are undertaken than on other PDE families. According to the research, very effective PDE9 inhibitors, PDE9-I, decrease multi-organ lipid buildup by enhancing lipolysis and mitochondrial respiration (25,26).

Conclusion

Insulin-like peptide 5(INLP5) could play in role in prompting insulin resistance (IR). Phosphodiesterase 9 (PDE9) is a regulator of energy, that inhibition of (PDE9) association with increase the occurrence of insulin resistance.

Recommendation

Based on the suggestion that PDE suppresses obesity, it is preferable to study it in women after and before menopause to confirm the relationship, additionally, we recommend studying the IL5 level in diabetic patients to give a clear idea of its relationship to insulin resistance.

Acknowledgments

We would like to thank the field and laboratory technicians at Baghdad University, college of medicine, Department of Biochemistry for their assistance in this project.

Funding

This research did not receive any specific fund.

Conflict of Interest

The authors declare that they have no competing interests.

Data availability

Data are available upon reasonable request.

ORCID

Zuhair Hussein 0009-0002-2817-2456
Maysaa Majeed 0009-0002-8884-6715
Lubna Al-Anbari 0000-0001-5576-9579
Suzan Al-Naqeeb 0000-0002-4736-8967

References

https://doi.org/10.21123/bsj.2022.19.2.0340
https://doi.org/10.1006/geno.1999.5899
https://doi.org/10.2147/DMSO.S247379
https://doi.org/10.1038/310775ai
https://doi.org/10.1016/j.bbrc.2011.02.042
https://doi.org/10.47723/kcmj.v19i3.999
https://doi.org/10.1016/j.mce.2013.08.010
https://doi.org/10.1007/s00726-015-2144-5
https://doi.org/10.1124/jpet.111.191353
https://doi.org/10.1186%2F1471-2210-11-S1-O29


To cite this article: Hussein ZA, Majeed MJ, Al-Anbari LA, Al-Naqeeb SAR. The Association between the Levels of Phosphodiesterase 9, Insulin-like peptide 5 and Obesity in Women. Al-Kindy College Medical Journal. 2024;20(2):117-121. https://doi.org/10.47723/6btq4431