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The potential effect of Tirzepatide (Mounjaro) on Leptin hormone and some biochemical markers in Obese Iraqi individuals

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Abstract

Tirzepatide is a once-weekly injectable medication that acts as a dual incretin receptor agonist, stimulating glucose-dependent insulin release, reducing hepatic glucagon production, slowing gastric emptying, and inducing satiety. The U.S. Food and Drug Administration (FDA) approved Mounjaro (tirzepatide) injection on May 13, 2022, for improving glycemic control in adults with type 2 diabetes (T2D). It is a very good alternative for the treatment of T2D because of its strong weight-loss benefits and high glycemic-lowering efficacy. The study aimed to assess the impact of the weight loss drug tirzepatide on leptin and some biochemical parameters before and after three months of treatment. Blood samples were collected from 50 people aged 25 to 65 years who had been receiving tirzepatide for at least 3 months as part of their obesity treatment. Participants in the study were placed on a low-calorie diet and tirzepatide treatment plan, starting at 2.5 mg/day in the first month, 5.0 mg/day in the second month, and increasing to the target dose of 10 mg/day in the third month. Leptin levels and some biochemical markers were measured before and after three months of treatment with tirzepatide. Results indicated that none of the participants experienced pancreatic or thyroid disorders during the trial. After three months, significant reductions were observed in weight, body mass index (BMI), Fasting blood glucose (FBG), thyroid stimulating hormone (TSH) and an increase in leptin levels. Additionally, the results revealed an increase in leptin levels and a decrease in TSH levels after treatment with tirzepatide, which may be an indication of a relationship between the drug and leptin. Metabolic measurements, including weight, body mass index, blood sugar, and glycated hemoglobin (HbA1c) levels, also showed improvement.

Keywords: Mounjaro, Tirzepatide, leptin hormone, obesity, biochemical markers.

التأثير المحتمل لدواء تيرزيباتيد (مونجارو) على هرمون الليبتين وبعض المؤشرات البيوكيميائية لدى الأفراد العراقيين المصابين بالسمنة

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الخلاصة

تيرزيباتيد دواء يُحقن مرة واحدة أسبوعيًا ويعمل كمُحفِّز لمستقبلات الإنكريتين حيث يُحفِّز إفراز الأنسولين المعتمد على الجلوكوز ويُقلِّل إنتاج الجلوكاجون الكبدي ويُبطئ إفراغ المعدة ويُحفِّز الشعور بالشبع. وقد وافقت إدارة الغذاء والدواء الأمريكية (FDA)على حقنة مونجارو (تيرزيباتيد) في 13 مايو 2022، لتحسين ضبط نسبة السكر في الدم لدى البالغين المصابين بداء السكري من النوع الثاني (T2D). وهو بديل ممتاز لعلاج داء السكري من النوع الثاني نظرًا لفوائده الكبيرة في إنقاص الوزن وفعاليته العالية في خفض نسبة السكر في الدم. هدفت الدراسة إلى تقييم تأثير دواء تيرزيباتيد لإنقاص الوزن على اللبتين وبعض المعايير الكيميائية الحيوية قبل وبعد ثلاثة أشهر من العلاج. جُمعت عينات دم من 50 شخصًا تتراوح أعمارهم بين 25 و65 عامًا ممن تلقوا تيرزيباتيد لمدة 3 أشهر على الأقل كجزء من علاجهم للسمنة. وُضع المشاركون في الدراسة على نظام غذائي منخفض السعرات الحرارية وخطة علاجية باستخدام تيرزباتيد بدءًا من 2.5 ملغ/يوم في الشهر الأول و5.0 ملغ/يوم في الشهر الثاني وزيادة الجرعة المستهدفة إلى 10 ملغ/يوم في الشهر الثالث. تم قياس مستويات اللبتين وبعض المؤشرات الكيميائية الحيوية قبل وبعد ثلاثة أشهر من العلاج باستخدام تيرزباتيد. أشارت النتائج إلى أن أياً من المشاركين لم يُعانِ من اضطرابات في البنكرياس أو الغدة الدرقية أثناء التجربة. بعد ثلاثة أشهر لوحظ انخفاض كبير في الوزن ومؤشر كتلة الجسم (BMI)ونسبة الجلوكوز في الدم أثناء الصيام (FBG)وهرمون تحفيز الغدة الدرقية (TSH)وزيادة في مستويات اللبتين. بالإضافة إلى ذلك كشفت النتائج عن زيادة في مستويات اللبتين وانخفاض في مستويات TSH بعد العلاج باستخدام تيرزباتيد مما قد يكون مؤشراً على وجود علاقة بين الدواء واللبتين. وأظهرت القياسات الأيضية بما في ذلك الوزن ومؤشر كتلة الجسم وسكر الدم، ومستويات الهيموجلوبين السكري (HbA1c)، تحسنًا أيضًا.

1. Introduction

Internal proteins called incretins regulate multiple body functions including blood sugar levels and stimulate the sensation of fullness [1]. Following their production by the lower gut's enteroglucagon produced by L cells in reaction to food consumption, incretins bind to a variety of receptors, including the pancreas, and trigger the release of glucose-dependent insulin, which lowers increased blood glucose levels. Other roles within and outside the pancreas are also performed by incretins [2].

Glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) are the two main incretin hormones present in the body [3]. Although glucagon-like-peptide-2 (GLP-2) is structurally similar, it is generally not classified as an incretin due to its lack of glycemic effects. GIP acts on pancreatic beta cells and, via class-II G-protein coupled receptors, reduces glucose by increasing intracellular cAMP and calcium to release insulin [4-7]. GIP also aids in the metabolism of lipids and stimulates the growth of beta cells [8]. GIP receptors are also found in various organs, including the skin, kidneys, and heart, however, it is unknown what role they serve [9-11].Similar to the action of GIP affecting the pancreas, GLP-1 binds to GLP-1 receptors and has a similar glycemic impact [12,13]. GLP-1 also inhibits the emptying of the stomach, reduces appetite, and lowers glucagon release, which lowers the amount of glucose produced internally [14]. Furthermore, GLP-1 has been shown to promote pancreatic beta-cell proliferation and shield beta-cells from apoptosis [15].

Tirzepatide is a glucose-dependent insulinotropic polypeptide and is given once a week. Australia, Canada, the United States, the United Kingdom, and the European Union have all given their permission to use it. Tirzepatide precise role in therapy is still being determined since research is still being done on how it affects major adverse cardiovascular events, diabetic renal disease, and heart failure, but its significant benefits on weight reduction and extremely high glycemic efficacy make it a desirable alternative for the treatment of T2D [16].The FDA authorized Mounjaro (tirzepatide) injection on May 13, 2022, to help people

with T2D achieve better glycemic control in addition to diet and exercise [17]. A first-in-class drug that stimulates the GLP-1 and GIP receptors is tirzepatide [18].

A tonic hormone that controls hunger, leptin is essential for the long-term maintenance of energy balance [19]. Based on available data, it appears that leptin is necessary for the typical orexigenic or anorexigenic response of many of these hormones that regulate appetite, such as ghrelin and cholecystokinin (CCK), require leptin to function whereas GLP-1 is required for leptin to function. These responses are modified when leptin injection or gene therapy is used in conjunction with these hormones or their agonists [20]. Given the complexity of the appetite-regulatory system, it is recognized that peptide tyrosine (PYY), brain-derived neurotrophic factor (BDNF), orexin-A (OXA), and amylin are linked to leptin. Reviews so far have focused on the roles that leptin plays in thermogenesis or the links that currently exist between it and the many neuropeptide modulators of hunger inside the central nervous system (CNS) [21,22]. Based on available data, leptin may have synergistic or antagonistic effects on appetite suppression when combined with the circulating peripheral appetite hormones ghrelin, GLP-1, CCK, OXA, and amylin. Although further investigation is necessary, leptin seems to be essential for energy intake as well as expenditure. More precisely, it seems that these activities depend on functioning leptin receptors [23]. The study aimed to evaluate the effect of the weight loss drug tirzepatide on leptin and some biochemical parameters before and after three months of treatment.

2. Subjects & Methods

The current study was carried out in compliance with the Declaration of Helsinki and authorized by the Ethics Committee of the Department of Basic Sciences, College of Dentistry, Mustansiriyah University.Fifty individuals, ranging in age from 25 to 65, participated in this investigation for 3 months. Before completing the third month of treatment, ten patients discontinued tirzepatide use. Among them, one patient reported nausea, two reported constipation and stomach discomfort, and seven patients cited financial difficulties as reasons for stopping. Of the remaining 40 patients, 8 had type 2 diabetes. In the last week of the final dosage, blood samples were taken from every participant who took tirzepatide for three months to reduce obesity. The study was carried out at the Al-Yarmouk Teaching Hospital / General Surgery Department in Iraq from April 2024 to August 2024.

Obesity was defined as having a Body Mass Index (BMI) of 30 kg/m2 or above [24]. All pancreatic disorders, thyroid or pituitary disorders, the use of drugs that influence the hypothalamic-pituitary-thyroid axis, thyroid surgery history, neck radiation history, liver and kidney diseases, and breastfeeding were among the exclusion criteria. A low-calorie diet and tirzepatide treatment plan were administered to all participants. The dosage was titrated to reach the goal dose of 10 mg/day over the course of three months: 2.5 mg/day in the first month, 5.0 mg/day in the second, and 10 mg/day in the third.

After all, participants fasted overnight, ten milliliters of blood were collected by venipuncture; 1.0 ml of whole blood was used in the determination of HbA1C% and the remaining portion was centrifuged for 15 minutes at 4000 rpm after being allowed to clot for 15 minutes at 37°C. The serum obtained was analyzed for fasting blood sugar, liver and kidney function tests, amylase, lipase, TSH, FT4, FT3 and leptin levels. In addition, height, weight, body mass index, patient age, sex and chronic diseases were measured. All these data were evaluated before/after 3 months of terzepatide treatment. Competitive ELISA Reveals (CER) was used to assess leptin levels. Electrochemical immunoassay (ECLIA) techniques were used to assess thyroid function tests (Cobas; Roche Diagnostics, Mannheim, Germany). The remaining parameters (F.B.G, liver and kidney function test) using (Roche Diagnostics' Cobas c311 analyzer Mannheim, Germany).

Statistical analysis

IBM SPSS was used to conduct the statistical analyses (version 29; IBM Corp., Armonk, USA). The study's findings were expressed as mean ± Standard Deviation (±SD). P-values were categorized as significant (S) if P value ≤0.05 or non-significant NS if P value (≥0.05).

3. Results

During the study period, 40 patients were treated with tirzepatide. Metabolic and laboratory parameters were compared before and after three months of treatment as shown in the tables below.

Table 1 indicates that most parameters, including weight, BMI, HbA1c, FPG, liver and kidney function tests, amylase activity and lipase activity, showed no significant changes pre- and post-treatment. However, BMI, FBG, and HbA1C showed a significant decrease after treatment.

Table 1: Biochemical parameters of patients for pre/post tirzepatide treatment

Parameters	Pre Tirzepatide Treatment	Post Tirzepatide Treatment	P-Value
BMI (kg/m^2)	40.2 ± 4.1	34.4 ± 4.2	S
F.B.G (70-115 mg/dL)	95.10 ± 8.246	84.20 ± 7.680	S
HbA1c (< 5.8%)	5.73±0.17	5.28±0.13	S
T.S.B (0.2 – 1.2 mg/dL)	0.82± 0.223	0.81± 0.264	NS
AST (< 40.0 U/l)	15.96 ± 4.011	16.21 ± 4.327	NS
ALT (< 41.0U/l)	15.88± 8.506	14.88± 5.925	NS
ALP (< 129U/l)	76.88 ± 26.417	74.55 ± 27.735	NS
GGT (16 – 73 U/l)	22.75 ± 6.146	23.01 ± 5.515	NS
Total Protein (6.6 – 8.7 g/dL)	7.70 ± 6.329	7.54± 6.165	NS
Serum albumin (3.5 – 5.0 g/dL)	4.43 ± 0.705	4.42 ± 0.718	NS
Urea (15 – 48 mg/dL)	27.41 ± 11.835	27.83 ± 11.093	NS
Creatinine (0.6 – 1.2 mg/dL)	0.86± 0.172	0.85 ± 0.170	NS
Uric acid (3.6 – 7.2 mg/dL)	5.18 ± 1.210	4.089 ± 1.243	NS
Amylase (37 – 125U/l)	46.4 ± 19.671	47.2 ± 20.627	NS
Lipase (< 60U/l)	37.1 ± 17.671	39.5 ± 14.342	NS

[25] reference to normal values within the table.

The FT3 and FT4 values presented in Table 2 showed no statistically significant. However, a statistically significant increase in serum leptin level and a decrease in TSH level were observed before tirzepatide treatment compared to after it.

Table 1: Levels of thyroid functions test and leptin hormone

Parameters	Pre Tirzepatide Treatment	Post Tirzepatide Treatment	P-Value
FT3 (2- 4.4 pg/Ml)	3.0 ± 0.7	3.01 ± 0.2	NS
FT4 (0.93-1.97 ng/Dl)	1.2 ± 0.4	1.2 ± 0.5	NS
TSH (0.27-4.20 Mu/Ml)	2.7 ± 1.1	2.0 ± 0.6	S
Leptin (0.5 – 12.5ng/mL)	2.92 ± 0.8	4.07 ± 1.06	S

4. Discussion

In the present study, after three months of tirzepatide treatment, a significant increase in leptin levels and a drop in TSH values in obese individuals. Thyroid hormone levels remained unchanged, while improvement in levels of metabolic parameters was detected.

Tirzepatide's several action pathways make it a useful medication for managing obesity [31]. After three months of therapy, a considerable improvement in metabolic indicators including weight, BMI, FPG, and HbA1c levels was observed. Ten individuals were unable to finish the third month of therapy because of gastrointestinal issues and associated costs. Due to its high cost, financial circumstances are the primary factor restricting the usage of tirzepatide.

Tirzepatide's effectiveness in reducing body weight was verified in SURMOUNT-2, a series of studies conducted by Eli Lilly Company, a group of individuals that contained individuals with T2DM and obesity. Following 72 weeks of tirzepatide (10 or 15 mg) medication, there was a significant difference in the groups' body weight changes from baseline and the percentage of people who lost 5%, 10%, or more while using tirzepatide compared to placebo, which is in agreement with the present study [26, 27]. Tirzepatide significantly reduced HbA1c levels when compared to placebo, and a higher percentage of subjects who received tirzepatide were able to stop taking their glucose-lowering drugs.

Tirzepatide has been demonstrated to significantly reduce the risk of developing T2DM. A post hoc analysis of SURMOUNT-1 revealed that in participants receiving tirzepatide, the 10-year predicted risk of developing T2D was reduced by up to 69% at week 72. This risk reduction was significantly greater compared to placebo, regardless of the participants' baseline glycemic status [28, 29].

Notably, the SURMOUNT trials also revealed improvements in patient-reported outcomes, with subjects reporting better physical functioning and better emotional and mental health scores when tirzepatide was used [30].

The effect of tirzepatide on the decrease of morbidity and mortality in persons with obesity who have established or elevated risk of cardiovascular disease is being studied in the SURMOUNT-MMO trial (NCT05556512) [31].

Conclusions

This study is the first in the literature to evaluate the weight-loss medication tirzepatide on leptin levels and select biochemical markers before and three months after treatment. Our findings revealed a significant increase in leptin levels and a significant decrease in TSH levels, but no change in thyroid hormone levels. Metabolic measures including weight, BMI, blood glucose, and HbA1c levels also showed improvement. More research with bigger sample sizes, longer follow-up times, and a causal link is required in this area. There are

several restrictions on our investigation. Both the study's participant count and follow-up duration were comparatively modest. In this sense, prospective multicenter trials with longer follow-up times and follow-up procedures following therapy withdrawal would be more instructive. Although the administration of tirzepatide may raise leptin levels and lower TSH levels, our study does not prove a causal relationship between these two.

6. Acknowledgements

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7. Ethical responsibilities of authors

This study was approved by the ethics committee of the college of dentistry, university of mustansiriyah.

8. Statements on compliance with ethical standards and standards of research involving animals

This article does not contain any animal studies conducted by the author.

9. Disclosure and conflict of interest

The author declares no conflicts of interest.

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