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Article

A Clinical Study on the Metabolic and Hormonal Effects of Terzepate in Women With Polycystic Ovary Syndrome and Obesity

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Abstract: Background: Polycystic ovary syndrome (PCOS) is an endocrine and metabolic dysfunction common in pre-menopausal women. Often linked to obesity, insulin resistance, hyperandrogenism, menstrual irregularities, and the risk for metabolic comorbidities. Relationship of obesity and insulin resistance in the pathophysiology and clinical presentation of PCOS is important. Tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist that has been shown to have significant weight and glycemic lowering effects. But there is very little evidence about its metabolic and hormonal effects specifically in women with PCOS. Hypothesis: The purpose of this study was to assess the effects of Tirzepatide treatment on women with PCOS and obesity, on their anthropometric, metabolic, hormonal and clinical parameters. Design: A retrospective observational study was carried out in 56 women with PCOS and obesity. The dose of Tirzepatide was initiated at 2.5 mg weekly, progressed to 5 mg weekly and then to 7.5 mg weekly as maintenance treatment. Baseline and post-treatment data included body weight, body mass index (BMI), fasting blood glucose (FBG), levels of glycated hemoglobin (HbA1c), insulin resistance, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), as well as certain clinical symptoms of PCOS. Paired statistical tests were used to analyze the continuous variables and the chi-square test was used to analyze the categorical variables. The p-value was determined and considered statistically significant at < 0.05. Results: It was observed that treatment was associated with significant reductions in body weight, BMI, fasting blood glucose and HbA1c. Mean body weight decreased from 84.80 ± 12.74 kg to 76.71 ± 10.84 kg ($p=0.0004$), while BMI decreased from 36.51 ± 6.14 to 32.49 ± 4.68 kg/m² ($p=0.0002$). Mean fasting blood glucose decreased from 6.89 ± 0.78 to 5.57 ± 0.42 mmol/L ($p<0.0001$), and HbA1c decreased from 5.7 ± 0.6% to 4.9 ± 0.4% ($p<0.0001$). Among respondents, 75.0% reported hormonal normalization for LH, 80.36% for FSH and 82.14% for testosterone. In 78.57% of patients, insulin resistance improved or normalized. There was also a significant reduction in other symptoms associated with PCOS such as acne, acanthosis nigricans, depression/anxiety, difficulty losing weight, ovarian cysts, sleep apnea and irregular menstruation. Conclusions: There was a marked improvement in anthropometric and glycemic parameters and in selected hormonal and clinical parameters in women with PCOS and obesity after treatment with tirzepatide. These results indicate that Tirzepatide has potential metabolic and clinical benefits in this population. The study was retrospective, small in size and followed patients for a relatively short duration, however, to

validate the results and establish long-term reproductive and safety outcomes, larger prospective, randomized controlled studies are needed.

Keywords: Polycystic ovary syndrome; Tirzepatide; GIP; GLP-1; obesity; insulin resistance; hyperandrogenism.

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous and endocrine and metabolic condition in women of reproductive age. It has reproductive, hormonal and metabolic abnormalities such as polycystic morphology of the ovaries, hyperandrogenism and ovulatory dysfunction. The Rotterdam diagnostic framework continues to be the most common and these three features should be present after ruling out other relevant disorders [1-4].

Obesity is a common comorbidity among women with PCOS, and is strongly correlated with insulin resistance, glucose intolerance, dyslipidemia, and enhanced cardiometabolic risk [5,6]. Insulin resistance is thought to be a key pathophysiological mechanism in PCOS and may play a role in hyperinsulinemia, excessive ovarian androgen secretion and decreased production of sex hormone-binding globulin in the liver. Such mechanisms may exacerbate hyperandrogenism and lead to ovulatory dysfunction and other clinical effects of the syndrome [7-10].

The metabolic dysfunction seen in PCOS has spurred a greater interest in obesity and insulin resistance treatment. Women with higher BMI are more likely to need to change their lifestyle as part of PCOS management. Lifestyle measures may be sufficient alone, but adding pharmacological interventions to address metabolic dysfunction can yield further benefit [11-15].

The effects of incretin-based therapies on body weight, glucose metabolism, appetite control, and insulin sensitivity have garnered much attention. GLP-1 receptor agonists have been shown to have beneficial effects on obesity and metabolic abnormalities and Tirzepatide is a new dual GIP/GLP-1 receptor agonist for treatment of type 2 diabetes and obesity [12,16,17].

Tirzepatide is a dual-acting glucagon-like peptide-1 receptor (GIP) and glucagon receptor (GLP-1) stimulator and has been linked to greater glucose-dependent insulin secretion, decreased appetite, delayed gastric emptying, and significant weight loss. The effects are especially prominent in the women who suffer from PCOS and obesity as obesity and insulin resistance are significant parts of the metabolic phenotype of PCOS.

International evidence-based guideline for PCOS 2023: anti-obesity drugs, including GLP-1 receptor agonists, may be considered as part of the management of higher weight in adults with PCOS (in addition to active lifestyle intervention). But the guideline also highlights the lack of long-term evidence and the need for individual decision making [18]. There are limited data, specifically for women with PCOS, that address Tirzepatide. The aim of the present study was therefore to assess the effect of Tirzepatide on metabolic, anthropometric, hormonal and clinical parameters in women with PCOS and obesity.

Materials and Methods

Study Design and Participants

This retrospective, observational study comprised of 56 women with PCOS and obesity who were followed at a private gynecology clinic in Iraq. The participants were referred for gynecological examination due to problems with their periods and other clinical signs and symptoms of PCOS. Data on the population and eligibility of the women included in the study was extracted from their medical records.

Eligibility criteria included age ≥18 years, diagnosis of PCOS, and obesity which was defined as BMI ≥30 kg/m² or BMI ≥27 kg/m² in the presence of obesity-related comorbidities. Patients excluded included pregnant women and women with known allergy to Tirzepatide as well as women with

significant renal, pancreatic disease, or ischemic heart disease. Other women who refused to take part were not included.

Tirzepatide Treatment

Tirzepatide was injected under the skin once a week. Upon initiation, the dose of treatment was 2.5 mg weekly for 4 weeks, then 5 mg weekly for 4 weeks followed by 7.5 mg weekly for the remaining week of treatment. The dose escalation approach was consistent with the principle of a gradual increase of dose to reduce gastrointestinal side effects from incretin-based therapy. All participants gave verbal informed consent prior to data collection.

Data Collection

Demographic and clinical data were collected from the medical record, and included age, comorbid conditions, and medication history. Laboratory records were reviewed to obtain metabolic and hormonal measurements.

The following variables were evaluated:

- Body weight
- Body mass index (BMI)
- Fasting blood glucose (FBG)
- Glycated hemoglobin (HbA1c)
- Where available, insulin resistance/HOMA-IR is measured.
- Liver enzyme levels
- Luteinizing hormone (LH)
- Follicle-stimulating hormone (FSH)
- Testosterone
- When available, ovarian ultrasound results;
- PCOS-related clinical symptoms

Data was collected at the beginning of Tirzepatide treatment and re-evaluated after Tirzepatide treatment. The primary results were body weight change, BMI change, glycemic control, insulin resistance, hormonal profile, symptoms of PCOS, and clinical outcomes in the treatment.

Clinical Assessment

Before and after clinical manifestations measured were irregular menstruation, acne, weight loss, insulin resistance-related symptoms, ovarian cysts, acanthosis nigricans, depression/anxiety, fatigue and sleep apnea.

Statistical Analysis

Data entered into a structured data collection form and analysed statistically. Continuous variables were represented as mean ± standard deviation (SD); categorical variables as frequencies and percentages. The changes between baseline and post treatment measures were assessed by paired comparisons. For categorical variables chi square test was used. A p value of < 0.05 was deemed as statistically significant.

Results

Anthropometric and Glycemic Outcomes

There was a notable decrease in body weight and BMI in patients treated with Tirzepatide. Mean body weight decreased from 84.80 ± 12.74 kg before treatment to 76.71 ± 10.84 kg after treatment ($p=0.0004$). Similarly, BMI decreased from 36.51 ± 6.14 to 32.49 ± 4.68 kg/m² ($p=0.0002$).

The mean percentage weight loss calculated is about 9.54% which is clinically relevant reduction in body weight. Other glycemic parameters were also considerably improved. Mean fasting blood glucose decreased from 6.89 ± 0.78 mmol/L before treatment to 5.57 ± 0.42 mmol/L after treatment ($p<0.0001$). HbA1c decreased from 5.7 ± 0.6% to 4.9 ± 0.4% ($p<0.0001$).

Table 1. Changes in anthropometric and glycemic parameters before and after Tirzepatide treatment

Parameter	Before treatment	After treatment	p-value
Body weight (kg)	84.80 ± 12.74	76.71 ± 10.84	0.0004
BMI (kg/m²)	36.51 ± 6.14	32.49 ± 4.68	0.0002
Percentage weight loss	—	9.54%	Clinically significant
Fasting blood glucose (mmol/L)	6.89 ± 0.78	5.57 ± 0.42	<0.0001
HbA1c (%)	5.7 ± 0.6	4.9 ± 0.4	<0.0001

The anthropometric and glycemic values were obtained from the study's reported results.

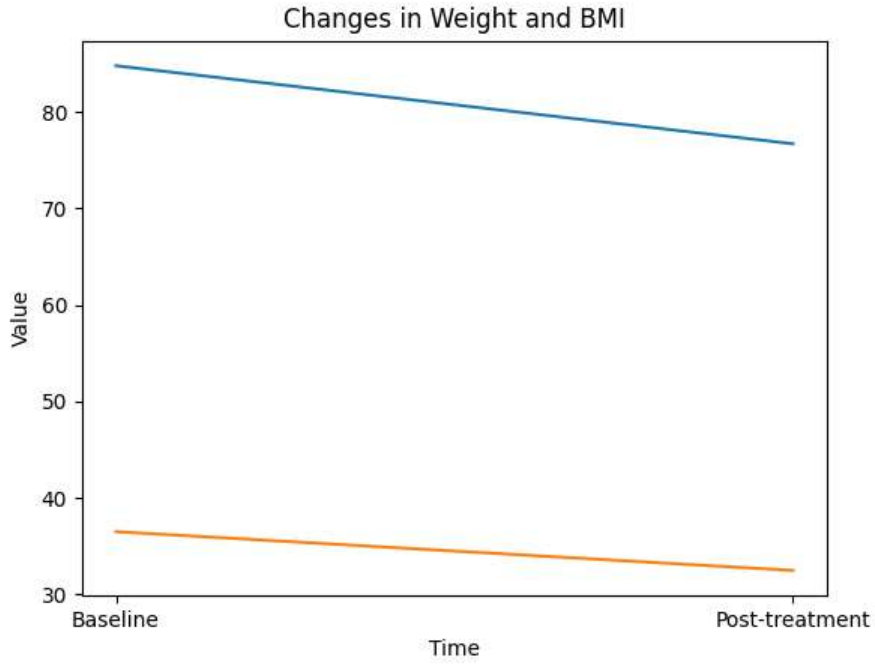

Figure 1. Changes in body weight and BMI following tirzepatide treatment

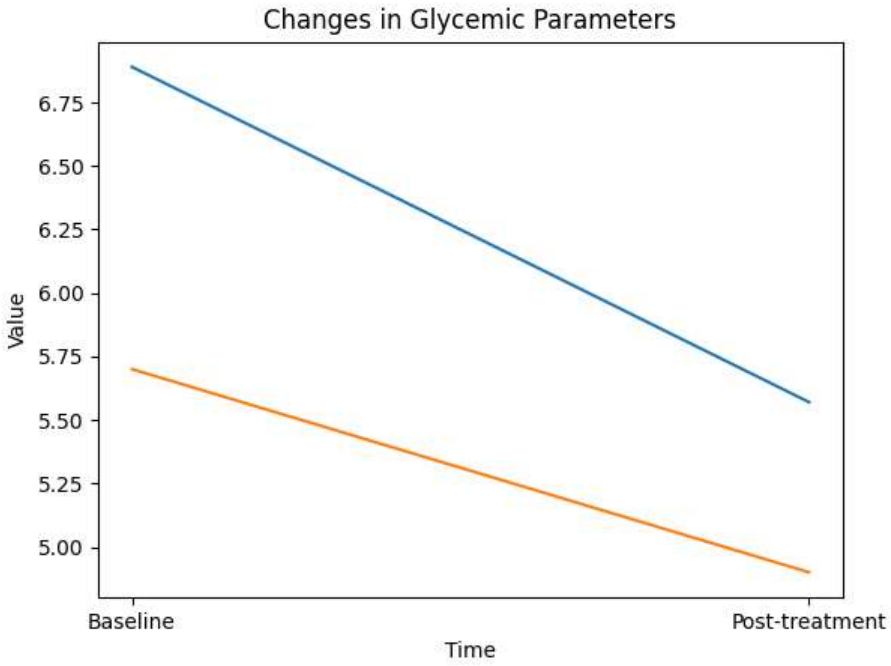

Figure 2. Changes in glycemic parameters including fasting glucose and HbA1c.

Hormonal Outcomes

After treatment, normalization of selected reproductive hormones was reported in a significant amount of the participants. The levels of LH were reported to be normalized in 75.00% of the participants, FSH in 80.36% and testiculer hormone in 82.14%. These results suggest improvement in the hormonal profile after treatment, but due to the retrospective study design, it is unclear if the treatment group specifically normalized these hormones.

Table 2. Hormonal changes following Tirzepatide treatment.

Hormonal parameter	Baseline status	Post-treatment finding	Outcome
LH	Elevated	6.18 ± 1.92 mIU/mL	75.00% normalized
FSH	Reduced/imbalanced	5.74 ± 1.61 mIU/mL	80.36% normalized
Testosterone	Elevated	38.26 ± 12.45 ng/dL	82.14% normalized

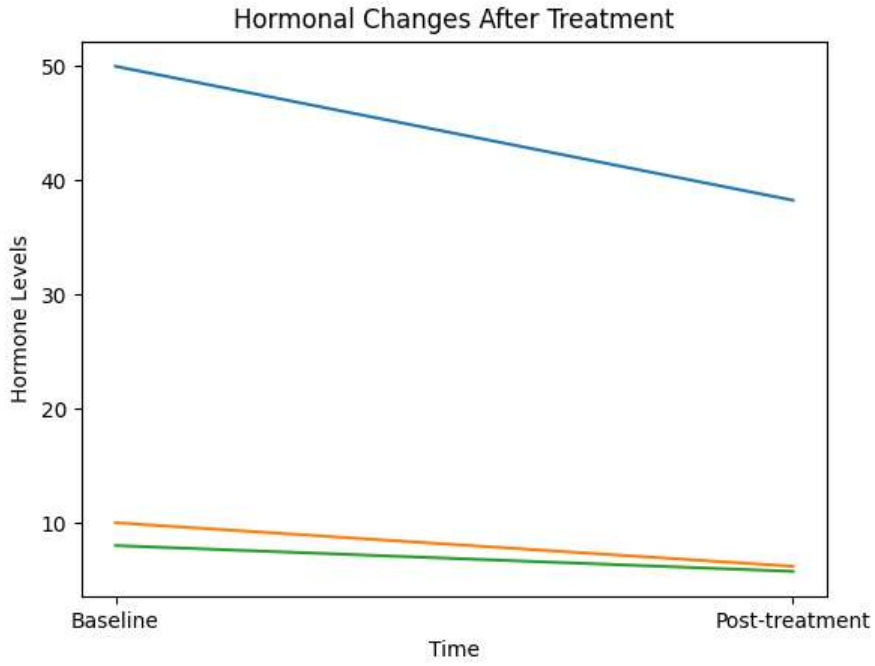

Figure 3. Hormonal changes including testosterone, LH, and FSH

Insulin Resistance

Insulin resistance was reported as increased at baseline and decreased after treatment. Overall, 78.57% of the participants had improvement in insulin resistance status (normalization or substantial improvement). This was consistent with results of the improvement in fasting blood glucose and HbA1c.

Clinical Symptoms of PCOS

Treatment resulted in a considerable decrease in several clinical manifestations related to PCOS. The percentage of women experiencing irregular menstruation went down from 85.7% to 32.1% ($p<0.0001$). Acne decreased from 67.9% to 33.9% ($p=0.0003$), while difficulty losing weight decreased from 100% to 16% ($p<0.0001$).

The percentage of patients with symptoms associated with insulin resistance dropped from 80.4% to 50.0% ($p=0.0008$). The percentage of women who had ovarian cysts dropped from 89.3% to 41.0% ($p<0.0001$). Acanthosis nigricans decreased from 50.0% to 21.4% ($p=0.0017$). Depression/anxiety (71.4% to 39.3%, $p=0.0007$) was found to decrease. Fatigue decreased from 62.5% to 42.9% ($p=0.038$), while sleep apnea decreased from 57.1% to 32.1% ($p=0.021$).

Table 3. Changes in PCOS-related clinical manifestations

Clinical manifestation	Before treatment (%)	After treatment (%)	p-value
Irregular menstruation	85.7	32.1	<0.0001
Acne	67.9	33.9	0.0003
Difficulty losing weight	100.0	16.0	<0.0001
Insulin resistance symptoms	80.4	50.0	0.0008
Ovarian cysts	89.3	41.0	<0.0001
Acanthosis nigricans	50.0	21.4	0.0017
Depression/anxiety	71.4	39.3	0.0007
Fatigue	62.5	42.9	0.038
Sleep apnea	57.1	32.1	0.021

The clinical symptom frequencies and p-values are based on the reported study data.

Discussion

PCOS is a complex endocrine-metabolic condition, where reproductive dysfunction, hyperandrogenism, insulin resistance and metabolic risk are interacting. The current study found that women with PCOS and obesity had significant reductions in anthropometric, glycemic, hormonal and clinical parameters after Tirzepatide therapy.

The most significant results included a decrease in body weight and BMI. The mean body weight dropped around 8.09 kg or 9.54% after the body weight was reported. BMI also decreased significantly from 36.51 ± 6.14 to 32.49 ± 4.68 kg/m². These findings are of clinical significance as managing weight is a significant part of the treatment of PCOS especially in obese women. The 2023 international guideline on PCOS includes pharmacological anti-obesity treatment as an option to consider in addition to lifestyle change in adults with PCOS and overweight [18].

The decrease in fasting blood glucose and HbA1c was also significant. Fasting blood glucose decreased from 6.89 ± 0.78 to 5.57 ± 0.42 mmol/L, while HbA1c decreased from 5.7 ± 0.6% to 4.9 ± 0.4%. The results are biologically plausible as Tirzepatide is known to activate both GIP and GLP-1 receptors and enhance glucose-dependent insulin secretion and metabolic control. The benefit on glycemic parameters is especially significant in PCOS as insulin resistance is a significant metabolic characteristic of the syndrome [7,9,16].

Of the participants, 78.57% experienced improved or normal insulin resistance. The observed changes in androgen-related and reproductive parameters could have been due to enhanced insulin sensitivity. Hyperinsulinemia may increase the production of ovarian androgens and decrease hepatic sex hormone binding globulin (SHBG) which increases the action of circulating androgens [4,7,9]. But, since metabolic status can indirectly affect reproductive endocrine function, improvement in this status could also indirectly result in improvement in reproductive endocrine function.

In the majority of the population studied, hormone results indicated a return to normal for levels of LH, FSH and testosterone. 82.14% of the participants had normalization of testosterone, 75.00% had normalization of LH and 80.36% had normalization of FSH. The results indicate that there may be a link between improvement in metabolic status and reproductive endocrine function. Based on the limitations of the present study, which is retrospective with no control group, it is not possible to determine if these hormonal changes were directly due to Tirzepatide, or if they were secondary to weight loss and improved metabolic health.

The clinical results also were good. The proportion of subjects with menstrual irregularity went down from 85.7% to 32.1%, while the proportion of subjects with acne went down from 67.9% to 33.9%. There was also a report of decrease in frequency of ovarian cysts and Acanthosis nigricans. Changes in these symptoms may be due to a combination of weight loss, hormonal sensitivity and androgen metabolism.

The reported decrease in depression and anxiety and fatigue may be important as psychological symptoms and diminished quality of life are known characteristics of PCOS. The implications of these results should be taken with a degree of caution, however, as there was no description of validated psychological assessment tools used. Therefore, it is recommended that future

research use standard scales to assess if metabolic treatment is able to measurably improve psychological well-being.

The results of the present study corroborate the general idea that obesity and metabolic dysfunction can be managed to alleviate a number of features of PCOS. However, the international guidelines up to now do not set Tirzepatide as a specific, already well-established therapy for PCOS itself. Alternatively, general obesity management guidelines may be applied to PCOS in adults who have greater weight who may benefit from anti-obesity medications [18].

There are a number of caveats to consider. A first limitation of the study is the retrospective observational study design, which restricts the ability to make causal inferences. Second, the size of the sample was relatively small (N = 56). Third, the study took place in one clinic, and thus the results cannot be extrapolated to other populations. Fourth, the follow-up period was relatively short and long-term reproductive outcome, such as ovulation and fertility, were not well evaluated. Lastly, the study lacked a placebo, lifestyle intervention and another proven metabolic therapy group.

However, these results offer initial proof that PCOS women with obesity receiving Tirzepatide therapy could experience significant benefits in metabolic and selected clinical parameters. Larger, prospective randomized controlled trials are needed to assess the consistency of the observed hormonal and reproductive effects, and to see if these effects would lead to better ovulation, fertility, and long-term cardiometabolic health.

Conclusion

In the present study, there was a significant improvement in body weight, BMI, fasting blood glucose, HbA1C, insulin resistance, selected reproductive hormones, and selected clinical manifestations of PCOS among women with obesity after Tirzepatide treatment. Significant improvements in glycemic control were seen, with a decrease in mean body weight of about 9.54%. A significant number of patients had hormonal normalization for LH, FSH and testosterone and insulin resistance had improved in 78.57% of the study population. Some of the additional symptoms associated with PCOS that reduced after treatment included menstrual irregularity, acne, difficulty losing weight, ovarian cysts, acanthosis nigricans, depression/anxiety, fatigue, and sleep apnea.

In conclusion, these results indicate that Tirzepatide has a potential role in the treatment of women with PCOS and obesity for metabolic purposes, especially in relation to weight and glucose metabolism. But the findings must be regarded with caution due to the retrospective design, limited sample size, lack of control group and short follow-up time. To assess long-term efficacy and safety of Tirzepatide in PCOS, and to determine its effect on ovulation, menstrual regularity, androgen levels, fertility, pregnancy outcomes and cardiovascular risk, additional large-scale, multicenter randomized controlled trials are recommended.

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