



Review of the Potential Effects of Semaglutide and Metformin in the Management of Polycystic Ovary Syndrome (PCOS) and Obesity

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Abstract

Polycystic ovary syndrome (PCOS) is considered a lifestyle disorder. Various lifestyle factors hinder obesity and insulin resistance, which worsen the symptoms of PCOS and this makes existing treatment very challenging. This review examines 10 studies on the effectiveness of combining glucagon-like peptide-1 (GLP-1) receptor agonists, particularly liraglutide and semaglutide, with metformin for weight control in women with PCOS. Results declared that combined therapy gives greater effects in terms of weight loss and metabolic improvement. Combined liraglutide with metformin led to an average weight reduction of 6.5 ± 29.55 kg and side-by-side reductions in body mass index (BMI), fasting glucose and insulin levels over 12 weeks. While comparing the monotherapy of metformin and liraglutide, liraglutide was more effective for weight loss, but the combination is thought to be impactful. Semaglutide monotherapy also emerged as a strong alternative, achieving a 9 kg weight reduction within 12 weeks in obese PCOS patients and was well-tolerated with minimal side effects. These findings suggest that combining semaglutide with metformin may be an effective approach for weight and metabolic issues in PCOS women, with semaglutide offering additional promise. Further studies are encouraged to refine dosing and explore long-term benefits.

Key words: Polycystic ovary syndrome; Obesity; Glucagon-like peptide-1 receptor agonists; Semaglutide; Liraglutide; Metformin.

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Citation:

Kaur P, Solanki R, Manocha N, Gautam RK, Chopra H. Review of the potential effects of semaglutide and metformin in the management of polycystic ovary syndrome (PCOS) and obesity. Scr Med. 2025 Nov-Dec;56(6):1239-47.

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Received: 22 March 2025

Revision received: 14 July 2025

Accepted: 15 July 2025

Introduction

Polycystic ovary syndrome (PCOS) is a prevalent endocrine illness that impacts women of reproductive age worldwide.¹ In 2012, the World Health Organization estimated that 3.4 % of women globally had PCOS. By 2023, the prevalence was estimated to affect 8–13 % of women of reproductive age. This significant increase underscores the critical importance of understanding and treating this condition.

The European Society for Human Reproduction and Embryology (ESHRE/ASRM) and the American Society for Reproductive Medicine (ASRM) have collaborated to provide a more accurate description of PCOS.^{2,3} This diagnosis, which rules out other potential causes, emphasises the existence of two of the three requirements listed below: (i) oligo-and/or anovulation, (ii) polycystic ovaries and (iii) clinical and biochemical hyperandrogenism.⁴

One of the most concerning aspects of PCOS is its strong association with obesity and insulin resistance. It has been observed that 60 % to 80 % of women with PCOS in developed countries such as the United States and Australia are either overweight or obese.⁵⁻⁹ Obesity not only exacerbates the hormonal imbalances typical of PCOS but also worsens clinical outcomes such as infertility, hirsutism and menstrual irregularities.^{5, 10-12} Women with PCOS who are obese are frequently connected with insulin resistance and hyperinsulinemia, which may be a major factor in favouring hyperandrogenism.¹³ Reduced sex hormone-binding globulin, increased glucose absorption, increased oestrogen synthesis and elevated hypothalamic-pituitary-adrenal axis and opioid system activity are further factors associated with obesity in PCOS.¹⁴

Managing weight and improving insulin sensitivity are, therefore, central to effective PCOS treatment. While metformin—a biguanide antihyperglycemic agent—has long been used as a first-line pharmacological intervention for its insulin-sensitising effects, recent attention has shifted to glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as semaglutide. These agents, initially approved for type 2 diabetes and obesity management, offer promising benefits in PCOS due to their ability to promote weight loss and improve glycaemic control.¹⁵

Emerging evidence suggests that a combination of semaglutide and metformin may provide synergistic effects, potentially offering greater improvements in metabolic and reproductive outcomes than either agent alone. These existing treatments often focus on treating PCOS symptoms that come with some adverse effects. However, there is a need to systematically assess and synthesise the available data to determine the efficacy of this combination therapy specifically in women with PCOS and concurrent obesity.

Metformin

Biguanides like metformin are frequently used to treat PCOS because of their capacity to enhance glucose absorption and utilisation, which lowers insulin resistance. Its effects on PCOS specifically include:

1. Regulating glucose levels: Metformin boosts peripheral glucose uptake while inhibiting mitochondrial complex I and reducing hepatic glucose synthesis and intestinal glucose absorption. The complete

control of glucose avoids both hypo- and hyperglycemia^{16, 17}

2. Hormonal balance: Metformin decreases androgen synthesis and raises SHBG, which lowers free testosterone levels via lowering insulin levels and CYP17 cytochrome activity. Menstrual periods are more regular as a result of this.^{1, 16}
3. Impact on menstrual cycle and obesity: Metformin is helpful for obese PCOS patients as it helps restore normal menstrual cycles and supports weight control by lowering androgen levels and increasing insulin sensitivity.^{16, 18} However, as a supplement to changing one's lifestyle, its impact on weight loss is frequently insufficient.¹⁹ Therefore, Metformin should be combined with a potential drug to outweigh the effects of weight loss in obese PCOS patients.

Glucagon-like peptide-1

GLP-1 analogues have just lately become popular as a type 2 diabetes mellitus medication.²⁰ In addition to their main function of enhancing glucose homeostasis, these drugs have also shown promise in decreasing body weight, which makes them useful in treating obesity linked to diseases such as PCOS.¹⁴

Mechanism of action. GLP-1 receptor agonists cause weight loss in many ways. They primarily slow down the emptying of the stomach by acting directly on the hypothalamus and postpone it by acting through the autonomic nervous system. Studies have shown that even individuals who do not experience nausea also benefit from losing weight, even though nausea is a typical side effect that may help with weight loss.²¹ The study highlights the noteworthy and long-lasting reduction in weight that obese individuals, regardless of their diabetes status, can accomplish with GLP-1 receptor agonists.²⁰ GLP-1 receptor agonists show promise as useful treatments for PCOS-afflicted women in controlling obesity, thereby addressing a crucial component of the condition. Recent developments in GLP-1 receptor agonists have brought attention to two medications that are useful in treating obesity and PCOS; semaglutide and liraglutide. Interestingly, semaglutide seems to have a higher potential for therapeutic benefits.

1. **Liraglutide.** Liraglutide is a long-acting GLP-1 analogue that may be administered subcutaneously once daily. Its half-life is 13

hours and it shares 97 % of the same amino acid sequence as human GLP-1. Liraglutide was first created to treat type 2 diabetes mellitus in conjunction with lifestyle therapy and oral antidiabetic medications. However, it has also demonstrated notable advantages in weight control. Even though metformin is a well-established treatment for PCOS, some research suggests that liraglutide, when taken with metformin, can help with obesity and PCOS. However, liraglutide has some side effects and is only available as an injectable, which may limit its suitability for patients and ultimately lower patient compliance.²²

2. Semaglutide. The only GLP-1 receptor agonist that comes in injectable and oral forms is semaglutide. The problem of poor absorption of peptides taken orally has been solved by combining sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) with semaglutide, an absorption enhancer. By acting as a local buffer, SNAC shields semaglutide and makes it easier for it to pass through the stomach epithelium. The European Medicines Agency (EMA) authorised *Rybelsus*, the first oral version of GLP-1 agonist semaglutide, in April 2020 after the FDA cleared it in September 2019.²³

Oral semaglutide has a poorer bioavailability than the subcutaneous formulation, hence a greater dosage of 7–14 mg/day is needed, as opposed to 1–2 mg/week for the subcutaneous formulation. Because oral semaglutide effectively improves glycaemic control, it is mostly used to manage type 2 diabetes.^{24, 25} On the other hand, semaglutide in an injectable form, usually administered at a dose of 1 to 2 mg weekly, is primarily used to treat obesity due to its substantial ability to reduce body weight.²⁴ Given its notable effectiveness in reducing weight, semaglutide is a desirable treatment for obesity in women with PCOS. Semaglutide may provide a strong treatment approach for PCOS-related obesity when combined with metformin, however further research is required to substantiate its efficacy in this group.²⁰

This review aimed to critically assess the efficacy of combined therapy involving semaglutide and metformin in promoting weight loss among patients diagnosed with PCOS. Through a comprehensive assessment of existing literature, the collective impact of these pharmacological interventions on weight management within the context of PCOS was analysed.

Methods

Search strategy

A thorough literature search was carried out across several databases, including *PubMed*, *Google Scholar* and *Elsevier*. Finding pertinent research published between 2010 and 2024 was the goal of the search. Search terms included: "PCOS", "GLP-1 receptor agonists", "metformin", "weight loss", "liraglutide", "obesity", "oral semaglutide" and "semaglutide". Only English-language publications were included in the search. The main database thought to reflect globally indexed publications worldwide was *PubMed*.

The inclusion and exclusion criteria

Studies involving women diagnosed with PCOS, as defined by the Rotterdam criteria and associated with obesity (body mass index (BMI) > 25 kg/m²), studies examining the short-term combination treatment of liraglutide and metformin and its impact on weight loss in obese women, studies investigating the use of semaglutide for weight management in obese PCOS patients who are not responding to lifestyle interventions were included in the analysis, observational studies and randomised controlled trials (RCTs) provided detailed data on the outcomes of interest; reviews, meta-analyses, case reports and studies directly related to the combination therapy of GLP-1 receptor agonists and metformin but not directly related to the combination of metformin and semaglutide in PCOS patients.

Study selection

Several steps were taken in the screening process to ensure that only top-notch research was included that was relevant to the review's objectives (Table 1). Every article that was found was screened for relevance regarding the use of GLP-1 receptor agonist and metformin combination therapy for PCOS weight loss in its titles and abstracts. Studies involving the GLP-1 receptor agonists semaglutide and liraglutide were given special attention during the screening process. The complete texts of studies that could be of interest were obtained and evaluated in the context of the inclusion and exclusion criteria. This review confirmed the inclusion of studies involving women aged 21–49 years diagnosed with PCOS based on the Rotterdam criteria, with a BMI > 25 kg/m² and examining the combination therapy of GLP1 receptor agonist and metformin.

Table 1: Prisma flow

Phase	Description	N
Identification	Records identified through database searching (eg <i>PubMed, Scopus</i>)	285
	Records identified through manual search (reference lists, grey literature)	30
	Total records identified	315
	Duplicates removed	10
	Records after duplicates removed	305
Screening	Records screened (title and abstract)	305
	Records excluded (irrelevant, off-topic, etc)	225
Eligibility	Full-text articles assessed for eligibility	80
	Full-text articles excluded with reasons:	50
	• No full text available	15
	• Irrelevant outcomes	20
	• Poor study design	11
Included	Studies included in the final review (qualitative synthesis)	29

Data were systematically extracted from the selected studies, focusing on the following outcomes: BMI (kg/m^2); body weight (kg), fasting glucose (mmol/L), insulin levels (mU/mL), homeostatic model assessment of insulin resistance (HOMA-IR). These outcomes were selected to examine the potential influence of combination treatment on weight reduction and metabolic improvements in PCOS patients.

od with a combination of metformin at a dose of 1000 mg BID and liraglutide at a dose of 1.2 mg QD subcutaneously. A decrease in BMI from $37.6 \pm 5.1 \text{ kg}/\text{m}^2$ to $35.3 \pm 5.5 \text{ kg}/\text{m}^2$ was observed in the participants, along with improvements in fasting glucose, insulin levels, which led to a lower HOMA-IR score.^{17,22}

Monotherapy vs combination therapy

Several studies examined the effectiveness of monotherapy of liraglutide and metformin and a combination of both therapies. Metformin 1000 mg BID is administered to 14 patients over the course of 12 weeks. According to this study (Table 3), over 12 weeks, metformin alone caused a modest $1.2 \pm 9.27 \text{ kg}$ weight loss; however, combined therapy produced a much larger weight decrease. Similarly, 11 patients treated with liraglutide monotherapy with a dose of 1.2mg QD subcutaneously generated a weight reduction of $3.8 \pm 20.45 \text{ kg}$, while the addition of metformin improved the weight loss to $6.5 \pm 29.55 \text{ kg}$, demonstrating a synergistic effect.

When compared to either medication alone the combined therapy also produced adverse effects. The COMB group of patients had headaches (3/11), sleeplessness (2/11), nausea (6/11) and diarrhoea (6/11). Three of them also experienced mild hypoglycaemia episodes. Liraglutide's gastrointestinal adverse effects were lessened by gradually titrating the dosage.²²

Potential of semaglutide

Semaglutide's identical pharmacological profile and weight-management efficacy made it avi-

Results

Overview of selected studies

Ten studies met the inclusion criteria for the review; these included prospective cohort studies, observational studies and RCTs; all of the studies focused on the effectiveness of liraglutide in combination with metformin and monotherapy of semaglutide for the management of weight and metabolic parameters in women with PCOS; the majority of the study participants were women aged 21–49 years, diagnosed with PCOS based on the Rotterdam criteria and with a BMI of more than $25 \text{ kg}/\text{m}^2$ (Table 2).^{22,26}

Combination therapy of liraglutide and metformin

Liraglutide and metformin together are an effective weight loss combination for PCOS-affected women, according to several studies. In Table 3 a RCT with 11 participants demonstrated a substantial weight reduction relative to baseline measures following a 12-week treatment peri-

Table 2: Baseline characteristic of participants undergoing different pretreatment regimens

Parameters	M (n = 14) Pretreatment	L (n = 11) Pretreatment	COMB (n = 11) Pretreatment	S (n = 21) Pretreatment
Body weight (kg)	103.2 ± 6.3	108.9 ± 15.1	105.5 ± 20.6	85 ± 15.0
BMI (kg/m ²)	36.6 ± 3.5	39.3 ± 4.2	37.6 ± 5.1	34.4 ± 5.9
Fasting glucose (mmol/L)	5.1 (0.9)*	5.1 (1.2)*	5.1 (0.2)*	5.4 ± 0.8
Insulin (mU/mL)	12.3 (13.3)*	11.1 (9.6)*	5.7 (11.8)*	17.0 ± 7.0
HOMA-IR	3.8 (3.8)*	2.4 (2.3)*	1.7 (4.9)*	3.5 ± 2.0

Data are presented as mean ± standard deviation and *median (interquartile range); BMI: body mass index; HOMA-IR: homeostasis model assessment of insulin resistance; M: metformin; L: liraglutide; COMB: combination therapy; S: semaglutide;

Table 3: Post-treatment characteristics of participants after 3 months across different regimens

Parameters	M (n = 14)		L (n = 11)		COMB (n = 11)		S (n = 21)	
	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment
Body weight (kg)	103.2 ± 6.3	102.0 ± 6.8	108.9 ± 15.1	105.1 ± 13.8	105.5 ± 20.6	99.0 ± 21.2	85.0 ± 15.0	76.0 ± 16.0
BMI (kg/m ²)	36.6 ± 3.5	36.1 ± 3.8	39.3 ± 4.2	37.9 ± 4.0	37.6 ± 5.1	35.3 ± 5.5	34.4 ± 5.9	30.8 ± 5.0
Fasting glucose (mmol/L)	5.1 (0.9)*	5.5 (0.5)*	5.1 (1.2)*	4.7 (1.0)*	5.1 (0.2)*	4.6 (1.0)*	5.4 ± 0.8	5.0 ± 0.4
Insulin (mU/mL)	12.3 (13.3)*	12.7 (8.3)*	11.1 (9.6)*	9.4 (9.6)*	5.7 (11.8)*	9.4 (11.7)*	17.0 ± 7.0	11.0 ± 5.0
HOMA-IR	3.8 (3.8)*	2.5 (2.4)*	2.4 (2.3)*	2.1 (2.0)*	1.7 (4.9)*	2.1 (2.9)*	3.5 ± 2.0	2.5 ± 1.0

Data are presented as mean ± standard deviation and *median (interquartile range); BMI: body mass index; HOMA-IR: homeostasis model assessment of insulin resistance; M: metformin; L: liraglutide; COMB: combination therapy; S: semaglutide;

able substitute for liraglutide. Semaglutide is quite effective at reducing body weight, according to studies (Table 3) on the therapy for obese PCOS women with increased body weight who are resistant to lifestyle changes. Twelve-week research with 21 PCOS patients who were also obese found that semaglutide, given subcutaneously once a week at a dose of 0.5 mg, resulted in an average weight loss of 9 kg.

Pretreatment values refer to initial measurements before the start of therapy and post-treatment values refer to measurements taken 3 months after the initiation of therapy.

Adverse effects. Patients in the COMB group experienced headache (3/11), insomnia (2/11), nausea (6/11) and diarrhoea (6/11), along with three minor hypoglycaemic events. The gastrointestinal side effects of liraglutide were lessened with gradual dose titration. The requirement for daily subcutaneous injections of liraglutide was generally not less desirable than the twice-daily oral application of metformin.²²

Merely nine individuals out of 21 reported morning nausea and two patients experienced occasional vomiting after receiving 0.5 mg of semaglutide once a week, indicating minor side effects.²⁶

This implies that compared to liraglutide, semaglutide medication alone had fewer adverse effects. The information suggests that the following factors make the combination of semaglutide and metformin seem preferable to the combination of liraglutide and metformin.

In contrast to the combination of liraglutide and metformin, the adverse effects of semaglutide are less severe. Compared to liraglutide's daily subcutaneous injections, semaglutide only needs to be injected once every week, making it a more convenient option. This is often more enticing to patients and may promote adherence to the treatment schedule.

Consequently, compared to the combination of liraglutide and metformin, the combination of semaglutide and metformin offers a more favourable side effect profile and higher convenience, making it a superior treatment option.

Evidence for weight reduction associated with PCOS by combined treatment of semaglutide and metformin

Both drugs work in different ways, but they might work together to help women with PCOS and obesity management. Metformin is mostly used to

improve insulin sensitivity in the treatment of type 2 diabetes and decreases the amount of glucose produced by the liver. Metformin aids in the restoration of normal menstrual periods by lowering testosterone levels and increasing insulin sensitivity. Its mild benefits on weight reduction are also linked to its effects on metabolic rate and hunger suppression.¹⁹

Semaglutide is a GLP-1 receptor agonist that slows stomach emptying, raises satiety and improves glucose-dependent insulin secretion. Clinical trials on semaglutide have demonstrated notable benefits for weight loss. They primarily slow down the emptying of the stomach by acting directly on the hypothalamus and postpone it by acting through the autonomic nervous system. Studies show that even patients who do not experience nausea benefit from losing weight, even though nausea is a common side effect that may contribute to weight loss.²⁷

Key findings indicate that using semaglutide alone results in significant weight loss and improves metabolic parameters with fewer side effects in women with PCOS, compared to the combination of liraglutide and metformin, which shows side effects in more than 50 % of the study population. Additionally, semaglutide improves patient compliance as it is administered once a week, whereas liraglutide requires daily administration for a week. These findings have clinical relevance and may help manage PCOS symptoms related to obesity, with semaglutide offering a promising alternative due to its substantial efficacy in weight management and improved adherence profile.

Overall, while the combined therapy of GLP-1 receptor agonists and metformin has substantial potential for treating obesity in PCOS patients, more extensive, long-term research is required to validate these results and provide complete treatment guidelines.

Discussion

Liraglutide and semaglutide, two GLP-1 receptor agonists, are primarily used to treat type 2 diabetes and obesity. By inhibiting glucagon release, boosting glucose-dependent insulin secretion, mimicking GLP-1 and delaying gastric emptying, they all work together to control

blood sugar levels and suppress hunger.²⁸ Due to their longer half-lives, semaglutide and liraglutide are usually injected weekly and daily, respectively, subcutaneously. Clinical trials have shown both drugs to cause significant weight reduction; however, semaglutide has proven to be significantly more effective, resulting in an average weight loss of 9 kg over three months as opposed to 3.8 ± 20.45 kg with liraglutide. While nausea and gastrointestinal problems are frequent side effects, both medications are usually well tolerated. Compared to liraglutide, which requires daily injections, semaglutide only needs to be taken once every week, which may lead to better patient adherence. Both drugs, which are marketed as *Saxenda* for liraglutide and *Wegovy* for semaglutide, have FDA approval for weight management in individuals who are obese or overweight and have diseases connected to their weight.²⁹

Semaglutide, due to its longer half-life, higher potency, enhanced efficacy in weight reduction and improved cardiovascular profile, may offer greater therapeutic advantages when combined with metformin compared to the combination of liraglutide and metformin. Additionally, its less frequent dosing schedule contributes to better patient adherence, which is a critical factor in chronic disease management.

For patients with obesity, particularly in the context of PCOS, these pharmacological benefits could translate into more effective weight control, improved glycaemic regulation and broader health outcomes. Based on existing evidence regarding the monotherapy effects of both semaglutide and metformin, the proposed combination therapy may hold enhanced clinical value.

Furthermore, it is important to note that treatment efficacy may vary across populations due to genetic, environmental and lifestyle differences—particularly when comparing Asian and Caucasian cohorts. These factors should be considered when interpreting potential clinical impacts and designing future studies involving this combination.

Need for future research

PCOS is strongly associated with insulin resistance, hyperinsulinemia and a high prevalence of obesity. Understanding the combined therapeutic potential of semaglutide and metformin is essen-

tial, given their individual roles in ameliorating insulin resistance and promoting weight loss. Both agents have demonstrated efficacy as monotherapies; however, their combined use in PCOS patients remains unexplored in clinical settings. It is hypothesized that their complementary mechanisms may address PCOS-specific manifestations such as menstrual irregularities, hyperandrogenism and infertility more effectively than either drug alone.

Despite their general tolerability as individual treatments, the safety and efficacy of their combination in PCOS populations warrant thorough investigation. Future studies should specifically focus on assessing the tolerability and therapeutic profile of semaglutide–metformin regimens, including their impact on reproductive and metabolic outcomes.

To ensure broader applicability and improve external validity, research should encompass diverse demographic groups, accounting for genetic, environmental and lifestyle differences across populations. Additionally, clinical trials are needed to identify optimal dosing strategies, evaluate long-term effects and determine the influence on overall quality of life. Elucidating the underlying synergistic mechanisms could inform the development of more targeted and effective PCOS therapies. Finally, expanding insurance coverage for these pharmacological options is crucial for enhancing accessibility and supporting equitable health outcomes among patients with PCOS.

Conclusion

The effectiveness of GLP-1 receptor agonists—liraglutide and semaglutide, in particular—in combination with metformin for weight loss in obese and PCOS women was methodically reviewed. Key findings show that compared to monotherapies of either medication alone, combination therapy combining liraglutide and metformin is much more successful in encouraging weight reduction and improving metabolic parameters. Over 12 weeks, the combination of liraglutide and metformin led to an average weight loss of 6.5 kg and a BMI decrease of 2.3 kg/m². With an average weight loss of 9 kg in a 12-week trial, semaglutide also

showed better weight reduction, indicating that it is a promising substitute for PCOS-related obesity management.

Ethics

This review article was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

Acknowledgement

We extend our heartfelt gratitude to the Indore Institute of Pharmacy for their support and resources. Special thanks to our mentors for their guidance.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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