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The Role of GLP-1 Receptor Agonists in the Management of Polycystic Ovary Syndrome: A Narrative Review

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Abstract

Background: Polycystic ovary syndrome (PCOS) is a common hormonal disorder among women of reproductive age. Insulin resistance and obesity are frequent components of this syndrome and further worsen the associated hormonal disturbances and infertility.

Aim: The aim of this narrative review is to explore the potential role of GLP-1 receptor agonists (GLP-1 RAs) in the management of women with PCOS, with particular focus on their effects on blood glucose fluctuations and excess body weight, both of which are important targets in PCOS treatment.

Methods: The literature search was conducted using the PubMed database in order to find articles reporting on the mechanism of action of GLP-1 RAs, the results of their use in PCOS treatment, and their adverse effects. The authors included articles published between 2020 and 2026.

Results: GLP-1 RAs exhibit pleiotropic metabolic effects, including the regulation of insulin and glucagon secretion, protective effects on pancreatic beta-cells, and modulation of appetite and energy intake. These mechanisms may contribute to the beneficial clinical outcomes

observed in women with PCOS. Current clinical studies and meta-analyses have demonstrated the positive effects of GLP-1 RAs on anthropometric parameters, glucose metabolism, and selected reproductive and hormonal functions, particularly when used in combination with metformin. Adverse effects associated with these agents are mainly gastrointestinal and generally diminish over the course of treatment.
Conclusions: GLP-1 RAs appear to represent a promising therapeutic approach for women with PCOS. However, further studies are required to evaluate the long-term effects of their use in this patient population.

Keywords: Polycystic ovary syndrome, GLP-1 RAs, liraglutide, insulin resistance, semaglutide, obesity, infertility.

Background

Polycystic ovary syndrome (PCOS) is a common hormonal disorder that affects females at their reproductive age. PCOS is diagnosed when at least two of the following features are present: ovulatory problems, signs of high androgen levels, or polycystic ovaries as detected by ultrasound examination [1]. Frequent symptoms of PCOS include acne, hirsutism, irregular menstrual cycles, and ovulatory dysfunction leading to infertility. PCOS is also associated with an increased risk of developing cardiovascular disease and endometrial cancer. These features make PCOS a significant clinical problem [2, 3].

Metabolic disturbances, including insulin resistance, are an important part of PCOS. Diseased women display resistance to insulin, independent of body weight [4, 5]. Insulin resistance is associated with higher insulin levels [5]. Hyperinsulinemia stimulates the ovarian theca cells to produce more androgens. At the same time, levels of sex hormone-binding globulin (SHBG) decrease, resulting in higher free androgen levels in the blood. These changes contribute to hyperandrogenism [5-7]. Elevated levels of free androgens promote the accumulation of visceral fat, which further contributes to insulin resistance [8]. Women with PCOS who are overweight or obese have a higher risk of impaired glucose metabolism [9].

Moreover, adipose tissue plays a significant role in the development of hormonal disturbances in the course of PCOS. Within this tissue, androgens are aromatized to estrogens. The estrogens produced during this process disrupt gonadotropin secretion [10, 11].

Dysfunctional adipose tissue (particularly visceral fat) is also associated with the chronic low-grade inflammation characteristic of PCOS. Inflammatory mediators released by adipose tissue stimulate androgen production in ovarian theca cells. Additionally, tumor necrosis factor alpha (TNF-α) promotes the proliferation of theca cells and further enhances androgen secretion. Chronic inflammation also contributes to the development of insulin resistance [12].

Consequently, treating insulin resistance and reducing excess body weight are important parts of PCOS management. The most common approaches include lifestyle interventions [13] and metformin therapy [14]. However, these strategies have some limitations. For many women, lifestyle changes can be difficult to maintain or insufficient to achieve the desired results [13], while metformin can cause side effects in some patients, especially gastrointestinal problems

[15, 16]. These challenges emphasize the need for other treatment options, particularly those that improve insulin sensitivity and metabolic health in women with PCOS.

In recent years, GLP-1 receptor agonists **(**GLP-1 RAs**)** have gained attention due to their ability to improve glycemic control, promote weight loss, and potentially improve hormonal and reproductive parameters in women with PCOS [17-19]. This review aims to summarize current evidence on the mechanisms of action, clinical efficacy, and safety of GLP-1 RAs in the treatment of PCOS.

Methods:

The aim of this narrative review is to summarize the current knowledge on the potential role of GLP-1 RAs in the treatment of women with PCOS. The literature search was conducted using the PubMed database. Articles published between 2020 and 2026 were considered for inclusion. The following terms were used: „PCOS", „insulin resistance", „GLP-1 receptor agonists", „liraglutide", „semaglutide".

Eligible articles included those addressing the role of insulin resistance and obesity in the pathophysiology of PCOS, the mechanisms of action of GLP-1 RAs, their clinical effects in women with PCOS, and the safety of their use. Review articles, randomized controlled trials, clinical trials, and meta-analyses were included.

Conference abstracts and articles published in languages other than English were excluded. Titles and abstracts were screened for relevance, and full texts of selected articles were subsequently reviewed.

Results

Mechanisms of Action of GLP-1 Receptor Agonists

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), also referred to as incretin mimetics or GLP-1 analogs, constitute a class of pharmacological agents used in the management of type 2 diabetes mellitus and obesity. Their mechanism of action mimics that of endogenous GLP-1, a peptide hormone produced in the gastrointestinal tract [11].

Endogenous GLP-1 has a short half-life (approximately 1–2 minutes) and is rapidly degraded by the proteolytic enzyme dipeptidyl peptidase-4 (DPP-4) [19]. In contrast to the natural peptide hormone, synthetic GLP-1 is less susceptible to breakdown by DPP-4, which results in a prolonged half-life. Most GLP-1 RAs are administered subcutaneously due to poor oral bioavailability, with semaglutide being the only agent currently available in an oral form [21].

Drugs belonging to the GLP-1 RAs class can be classified into two groups based on their structural characteristics. The group with a human GLP-1 backbone includes dulaglutide, abiglutide, liraglutide, and semaglutide, whereas the group containing an exendin-4 backbone includes exenatide and lixisenatide [22].

Drug	Route of administration	Dosing frequency
Exenatide	Subcutaneous	Twice daily
Exenatide extended-release (ER)	Subcutaneous	Once weekly
Lixisenatide	Subcutaneous	Once daily
Liraglutide	Subcutaneous	Once daily
Dulaglutide	Subcutaneous	Once weekly
Semaglutide (subcutaneous)	Subcutaneous	Once weekly
Semaglutide (oral)	Oral	Once daily

Table 1. GLP-1 RAs: routes of administration and dosing frequency [21].

Effects on the Pancreas

GLP-1 RAs bind to and activate the GLP-1 receptor and stimulate glucose-dependent insulin secretion from pancreatic islet beta cells. In addition, GLP-1 RAs suppress glucagon release by acting on pancreatic islet alpha cells. This leads to a reduced release of glucose from hepatic glycogen. GLP-1 RAs decrease blood glucose levels without the risk of hypoglycemia [11, 23, 24].

GLP-1 RAs also exert a protective effect on pancreatic beta cells. Medicines belonging to this group exert anti-apoptotic effects in the pancreas and stimulate the proliferation of pancreatic beta cells [25].

Effects on the central nervous system (CNS)

GLP-1 also acts at the level of the central nervous system [26]. GLP-1 RAs activate receptors located in the nucleus of the solitary tract, enhancing the activity of serotonergic neurons and increasing the feeling of satiety. Stimulation of GLP-1 receptors in the area postrema influences dopaminergic signaling, which may be associated with a reduced rewarding effect of food intake. In the paraventricular nucleus, GLP-1 reduces appetite by affecting the secretion of corticotropin-releasing hormone, oxytocin, and thyrotropin-releasing hormone [27].

Activation of GLP-1 receptors in the arcuate nucleus of the hypothalamus stimulates neurons producing pro-opiomelanocortin (POMC). Besides activating POMC neurons in the arcuate nucleus, GLP-1 RAs also indirectly reduce the activity of NPY/AgRP neurons by affecting K-ATP and TRPC5 channels in GABAergic neurons. As a result, these changes lead to a reduction in appetite [27-29].

In the lateral hypothalamus, it inhibits orexin-producing neurons. GLP-1 RAs also affect the mesolimbic reward system by decreasing dopamine release and attenuating the sense of reward associated with food consumption [27].

Additionally, GLP-1 RAs may influence nutritional habits and food preferences. Several studies reported reduced preference for sweet, fatty, and energy-dense foods during treatment, possibly due to

decreased hedonic eating [30].

Effects on the gastrointestinal tract

Treatment with GLP-1 RAs leads to delayed postprandial gastric emptying, preventing swift glucose entry into systemic circulation, a pivotal factor in postprandial glucose fluctuations [22, 31].

GLP-1 receptors are located in the myenteric plexus of the intestines and are linked to the G protein (GSα subunit). Once activated, they stimulate an enzyme called adenylyl cyclase. This leads to the production of cAMP and reduces vagal nerve activity [32]. In this mechanism, GLP-1 RAs suppress gastric and duodenal peristalsis. It also increases pyloric tone and decreases gastric acid production [30]. Moreover, feedback mechanisms within the gastrointestinal tract further suppress motility and fluid secretion [31-34].

Sustained treatment with long-acting GLP-1 RAs is associated with a reduced effect on gastric emptying over time, reflecting the development of tachyphylaxis. It is less pronounced in the case of short-acting preparations [31].

Effects on the Gut Microbiota:

Some studies have also suggested that GLP-1 RAs may influence gut microbiota composition. Their use has been associated with increased microbial diversity and changes in bacterial populations linked to improved metabolic profile and glucose homeostasis. These effects may partially contribute to the beneficial metabolic outcomes observed during treatment [35].

Effects on the hypothalamic-pituitary-ovarian (HPO) axis:

Some studies suggest that GLP-1 RAs may influence the hypothalamic-pituitary-ovarian axis both centrally and peripherally. Within the ovary, they have been shown to enhance granulosa cell viability, likely through anti-apoptotic effects and increased proliferation, which may support follicular development. There are also reports suggesting the role of GLP-1 receptor signaling in the regulation of ovarian steroidogenesis. However, most of these findings come from experimental models, and their clinical relevance remains uncertain. GLP-1 RAs may also act at the hypothalamic level and regulate pulsatile gonadotropin-releasing hormone (GnRH) secretion [36].

Organ/system	**Effects of GLP-1 RAs**
Brain	Increase the sense of satiety reduction in appetite
Liver	Decrease in liver glucose production Decrease in liver fat content Decrease in glycogenolysis
Pancreas	Increase in insulin synthesis Increase in insulin secretion Decrease in glucagon secretion Decrease in blood glucose level Increased proliferation of pancreatic beta cells Reduced beta-cell apoptosis
Gastrointestinal tract	Decreased gastric acid production

	Decrease in gastrointestinal peristalsis Decrease in gastric emptying
Heart	Decrease in blood pressure
Adipose tissue	Increase in lipolysis Increase in thermogenesis Increase in glucose uptake Increase in fatty acid synthesis
Muscle	Increase in glucose uptake Increase in glycogen synthesis
Others	Decreased triglyceride levels Decreased low-density lipoprotein cholesterol levels

Table 2. Effects of GLP-1 RAs on different organs and systems [11, 22-34].

Clinical Effects of GLP-1 RAs in PCOS

Effects on Anthropometric Parameters

Use of GLP-1 RAs in patients with polycystic ovary syndrome (PCOS) is associated with improvements in anthropometric parameters. Studies show that GLP-1 RAs use leads to reductions in body weight, BMI, waist circumference, body fat mass, and visceral fat mass [37].

Liraglutide is one of the most commonly studied GLP-1 RAs in this group of patients. The effects of liraglutide at a daily dose of 3 mg have been evaluated in obese women with PCOS without diabetes. After 32 weeks of treatment, reductions in mean body weight from 111 kg to 104.7 kg, with a corresponding reduction in BMI from 41.6 kg/m^2 to 39.1 kg/m^{2}have been observed. The mean percent weight loss exceeded 5% and reached 5.7%. Improvements in body composition were also observed. Dual-energy X-ray absorptiometry (DXA) measurements showed reductions in fat mass, with no change in lean body mass. Additionally, this treatment was effective in reducing central obesity, as evidenced by the decreases in both waist circumference (WC) and the waist-to-hip ratio (WHR) [38].

Weight loss was also observed in women treated with semaglutide 0.5 mg administered subcutaneously once weekly for three months. The study included women who had not achieved satisfactory results with previous lifestyle interventions. After three months of treatment, the mean weight loss was 7.6 kg, accompanied by a reduction in BMI of 3.1 kg/m^2. A weight loss exceeding 5% of the baseline body weight was observed in 80% of participants, with an average percentage reduction in body weight of 8.9%. After six months, the mean weight loss reached 11.5 kg, and the average BMI decreased from 34.4 to 29.4 kg/m^2 [39].

The cited studies are consistent with the findings of a recent meta-analysis evaluating the effectiveness of GLP-1 RAs therapy in women with PCOS. The analysis included 13 randomized controlled trials, including one discussed above. The results indicate a potential beneficial effect of this group of drugs on body weight reduction and BMI improvement, particularly in comparison with placebo and metformin. Another important observed effect was the reduction of visceral adipose tissue, reflected by a decrease in WC and WHR [40].

Effects on Metabolic Parameters

In obese women with PCOS without diabetes, treatment with liraglutide 3 mg was associated with lower glucose levels during the oral glucose tolerance test (OGTT) compared with women not receiving the drug. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) analysis also showed improved fasting insulin sensitivity. A decrease in triglyceride (TRG) concentrations and the TRG/HDL ratio was observed in this study [38].

Metabolic parameters also improved in women treated with semaglutide. Women taking this medication for three months experienced a decrease in fasting glucose, insulin, and HOMA-IR values [39].

The results of a recent meta-analysis further suggest that GLP-1 RAs may be beneficial in the treatment of insulin resistance in women with PCOS. Treatment with these agents was associated with lower glucose levels during the 2-hour OGTT. These findings highlight the effects of GLP-1 RAs on postprandial insulin secretion and glucose regulation. A modest decrease in fasting insulin levels and HOMA-IR was also observed. However, no clear superiority over metformin was observed in terms of fasting glucose reduction. In addition, the effects on lipid parameters appeared to be limited [40].

Effects on Hormonal Parameters

A 32-week treatment with liraglutide at a daily dose of 3 mg was associated with a reduction in the free androgen index in women with PCOS. As a result of this therapy, the menstrual cycles became more regular [38].

Hormonal changes were also observed in women treated for sixteen weeks with combined metformin and semaglutide therapy. These included decreases in estradiol, testosterone, free androgen index, anti-Müllerian hormone, and increases in SHBG and prolactin. Moreover, the natural pregnancy rate was significantly higher in the group of patients receiving combination therapy than in the group taking metformin alone [41].

A recent meta-analysis reported heterogeneous effects of GLP-1 RAs on hormonal parameters in women with PCOS. Treatment was associated with reductions in DHEAS, total testosterone, and FAI compared with placebo, although no clear advantage over metformin was observed. At the same time, no significant changes were found in SHBG or free testosterone levels [40].

A second meta-analysis evaluated the effects of GLP-1 RAs on reproductive outcomes, including pregnancy rate and menstrual cyclicity in women with PCOS. The analysis included studies in which GLP-1 RAs were used as monotherapy or in combination with metformin. An increased rate of spontaneous pregnancies was reported in women treated with GLP-1 RAs, whereas no significant effect on pregnancy rates following in vitro fertilization was observed. Improvement in menstrual cycle regularity was also reported, with longer treatment duration being associated with better outcomes. In addition, GLP-1 RAs treatment was associated with increased SHBG levels and decreased total testosterone concentrations, while no significant changes were observed in free testosterone, DHEAS, or FAI [42].

Safety

Most side effects reported by patients using GLP-1 RAs involve the gastrointestinal tract. These include nausea, abdominal pain, bloating, gastrointestinal reflux, vomiting, diarrhea, and constipation [43, 44]. Gastrointestinal disturbances tend to occur more frequently in older adults, smokers, individuals with impaired renal function, and people with lower body weight. Gastrointestinal side effects tend to increase with higher doses, so the dosage should be escalated gradually [21]. These symptoms are usually mild or moderate and tend to improve over time, and they do not have a significant impact on glycemic control [45]. Vomiting and diarrhea can lead to acute kidney injury caused by dehydration [21]. Another side effect of this therapy reported by patients is headache [38].

Studies have also shown an increased risk of gallbladder or biliary disease in patients treated with GLP-1 RAs [43, 46]. This may result from reduced gallbladder motility during treatment with GLP-1 RAs. In addition, these drugs inhibit cholecystokinin secretion, which further delays gallbladder emptying. It has been observed that the risk of developing gallbladder and biliary disease is higher in patients receiving higher doses of these medications and in those treated for longer periods, compared with individuals using lower doses or undergoing short-term therapy. Moreover, this risk appears to be further increased in patients who experience rapid weight loss during treatment with GLP-1 RAs [47].

These agents are associated with a low risk of hypoglycemia, although this risk increases when they are co-administered with other antidiabetic medications, including sulfonylureas or insulin [21].

Some patients treated with GLP-1 RAs show increased pancreatic enzyme levels (lipase and amylase), although the values usually remain within the normal range [48]. Studies do not support an association between using GLP-1 RAs and acute pancreatitis. However, GLP-1 RAs should be used with caution in patients with risk factors for acute pancreatitis or a history of acute pancreatitis [45, 48].

Treatment with GLP-1 RAs is contraindicated in patients with a family history of medullary thyroid carcinoma. At the same time, studies have not confirmed an association between the use of these drugs and the development of this cancer [46].

Subcutaneous administration of these agents may result in injection site reactions and erythema [21].

Discussion

GLP-1 RAs act on multiple pathways in the human body. Numerous studies have demonstrated their beneficial role in reducing excess body weight in women with PCOS. Weight loss observed in patients receiving these drugs may be related to their effects on appetite regulation. Reduced hunger and enhanced satiety contribute to lower food intake. Another mechanism contributing to lower energy intake is delayed gastric emptying after meals. In women with PCOS, not only weight reduction itself but also changes in body fat distribution, particularly a decrease in visceral adipose tissue, appear to be clinically important. Reductions in waist circumference and WHR observed during GLP-1 RAs therapy may contribute to improvements

in insulin resistance and chronic low-grade inflammation, both of which are important components of PCOS pathophysiology.

Their positive impact on glycaemic control has also been reported. Treatment has been associated with reductions in fasting glucose levels, improvements in HOMA-IR, and overall better glucose metabolism. GLP-1 RAs appeared to have a more pronounced effect on 2-hour glucose levels during OGTT than on fasting glucose levels. This may be related to their ability to modulate glucose-dependent insulin secretion by pancreatic beta-cells in response to food intake.

These effects result not only from direct actions on pancreatic function but also from weight loss. Reduction of visceral adipose tissue appears to play a particularly important role in the improvement of metabolic parameters.

Despite their beneficial effects on body weight, visceral adipose tissue, and multiple pathways, the available evidence regarding the effects of GLP-1 RAs on lipid profile remains limited and inconsistent. In some women, additional lipid-lowering therapy may be required to achieve adequate lipid control.

Due to the well-documented efficacy of GLP-1 RAs in reducing excess body weight and improving glycaemic control, GLP-1 RAs may be especially useful in women who are overweight or obese, particularly when insulin resistance or diabetes is also present. Reducing excess body weight and improving insulin sensitivity may help improve hormonal disturbances observed in women.

The use of GLP-1 RAs in women with PCOS may potentially exert beneficial effects on hormonal disturbances through reductions in adipose tissue and improvements in insulin resistance. However, the currently available evidence regarding the effects of these agents on hormonal parameters and reproductive function remains inconclusive and requires further evaluation in well-designed clinical studies. Some studies have shown that the addition of GLP-1 RAs to metformin therapy was associated with an increased rate of spontaneous pregnancies. Combination therapy with GLP-1 RAs and metformin also appears to be more effective than metformin monotherapy, which may be related to greater reductions in body weight and more favorable metabolic effects.

However, there is still a lack of data regarding the safety of these agents during pregnancy. Due to insufficient data on their excretion into breast milk, GLP-1 RAs should be used with caution in nursing mothers [21].

Adverse effects of GLP-1 RAs are generally mild and tend to diminish over time. Most patients consider them acceptable in light of the therapeutic benefits. A potential drawback for some female patients when using certain GLP-1 RAs is the need for subcutaneous administration. An alternative is to use agents available in oral form. However, injectable formulations often have the advantage of not requiring daily dosing [49].

Limitations

One of the limitations of this review is the limited availability of long-term studies evaluating the effectiveness of GLP-1 RAs in the treatment of PCOS-related disorders. There is also the

lack of studies comparing the efficacy of individual GLP-1 RAs in the treatment of this patient population.

Narrative reviews support the role of GLP-1 RAs as an effective and safe alternative to currently available treatment options for metabolic and hormonal disturbances associated with PCOS. Similar conclusions were drawn by Kourtidou C and Tziomalos K, who suggested that GLP-1RAs may be the pharmacotherapy of choice in women with PCOS who are obese or overweight [50].

However, despite the promising effects of pharmacological therapies, lifestyle interventions should remain the first-line treatment in women with PCOS. Pharmacological treatment may be considered in patients who do not achieve sufficient improvement with lifestyle modification alone.

Metformin therapy can improve insulin resistance and metabolic disturbances in women with PCOS. However, its effect on weight reduction is usually limited. GLP-1 RAs can be added to metformin to improve overall treatment effects. They may also serve as an alternative when metformin alone is insufficient.

The choice of therapy should always be made individually, based on the patient's needs and clinical situation.

Conclusions:

GLP-1 RAs act on multiple tissues and have beneficial effects, including reducing appetite, limiting postprandial glucose fluctuations, and exerting protective effects on the pancreas. Numerous studies have confirmed their effectiveness in improving anthropometric measures, as well as metabolic disturbances in women with PCOS. However, their effects on the improvement of hormonal disturbances and reproductive function require further studies. Treatment with these agents is generally associated with mild side effects, mainly involving the gastrointestinal tract. Overall, this review highlights GLP-1 RAs as a promising option in the management of PCOS.

Disclosure

Author Contributions

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