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Role and Efficacy of GLP-1 Receptor Agonists in the Management of Polycystic Ovary Syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder characterised by a constellation of reproductive, metabolic, and hormonal abnormalities. This review evaluates the mechanism of action and efficacy of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in managing PCOS by analysing relevant studies from multiple databases. The methodological approach involved systematic screening of studies assessing the impact of GLP-1RAs on metabolic parameters and hormonal profiles with comparisons drawn against the standard therapy of Metformin. The selected studies demonstrated that GLP-1RAs effectively improved insulin sensitivity, promoted weight reduction, and enhanced the hormonal profile in women with PCOS. However, variations in study design, sample sizes, and treatment durations posed challenges to direct comparison. Despite promising evidence supporting the metabolic and reproductive benefits of GLP-1RAs in PCOS, long-term data on safety and sustained efficacy remain limited. Further large-scale randomized controlled trials are needed to establish standardized treatment protocols and evaluate the long-term impact of these agents. This review highlights the potential of GLP-1RAs as an emerging therapeutic option in the comprehensive management of PCOS.

Keywords: pcos, glp1ra, hyperinsulinemia,

1. Introduction

Polycystic Ovary Syndrome (PCOS) is an endocrine disorder commonly found in women of reproductive age. Its presentation, or phenotype, can vary widely and encompasses a range of diagnostic criteria. The primary characteristics of PCOS include a range of androgen excess, ovulatory dysfunction, and polycystic ovarian morphology [1]. A significant feature of PCOS is hyperinsulinemia, which leads to increased secretion of androgens from the adrenal glands. Women with elevated insulin levels, regardless of whether the source is endogenous or exogenous, are more likely to have PCOS [1]. This condition exacerbates both metabolic and reproductive symptoms [2]. Additionally, obesity is a common characteristic associated with PCOS. Visceral adipose tissue contributes to insulin resistance and promotes inflammation, increasing the risk of cardiovascular diseases, dyslipidemia, and prediabetes in women with PCOS [3].

Polycystic ovary syndrome presents with various clinical manifestations depending on the individual features. Therefore, the treatment for PCOS should be customized to address the specific complaints and symptoms of each patient [1]. Regular healthy eating and physical exercise are essential for improving overall health and optimizing hormonal balance [2]. For individuals with excess weight, losing 5-10% of

body weight is considered a significant clinical improvement and can help regulate hormonal levels [4]. Pharmacological treatments, such as metformin and hormonal contraceptives, focus on addressing insulin resistance and menstrual irregularities. However, these medications come with limitations, including gastrointestinal side effects and an increased risk of blood clots [2].

Since the underlying pathogenesis of PCOS closely resembles that found in diabetes mellitus, medications designed to treat high blood sugar levels and obesity may also be effective in managing PCOS. Studies, such as the one by Li et al., indicate that combining GLP-1 agonists with metformin leads to enhanced pregnancy rates compared to using metformin alone [5]. GLP-1 receptor agonists (GLP-1RA), originally developed for treating type 2 diabetes, have shown promise in managing PCOS by improving hyperinsulinemia and promoting weight loss. Nevertheless, comprehensive, targeted therapies that address the underlying causes of PCOS are still under investigation.

Discussion

Role of GLP-1 Agonists: Mechanism of Action

GLP-1 (Glucagon-like peptide-1) agonists, also known as Incretin mimetics, are a class of medications used to treat diabetes. Incretins are hormones secreted in the distal part of the small intestine that stimulate insulin secretion by the pancreatic beta cells in response to elevated blood glucose levels [6]. They promote insulin release specifically when blood glucose levels are high, such as after a meal. They do not stimulate insulin secretion when glucose levels are low, which helps eliminate the risk of hypoglycemia [7,8]. These agonists are designed to mimic natural GLP-1 and have several metabolic effects. They help inhibit the release of glucagon when it is not needed [9], slow down gastrointestinal motility, and reduce calorie intake [2,10]. Additionally, GLP-1 agonists inhibit gastrointestinal motility, preventing rapid gastric emptying, which can aid in weight management. Animal studies suggest that GLP-1 agonists may enhance pancreatic beta cell function and increase their mass. In these ways, GLP-1 contributes to maintaining blood glucose homeostasis and reducing the fluctuations in blood glucose levels postprandially [11].

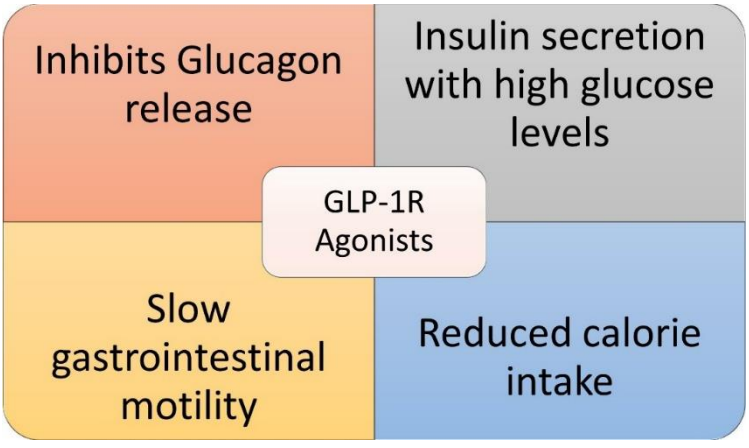

Figure 1: GLP-1R Agonists Mechanism of Action

The positive outcomes associated with GLP-1 receptor agonists (GLP-1RAs) have sparked considerable interest in their use for managing type 2 diabetes. These medications are already being utilized in the treatment of both type 2 diabetes and obesity. Research indicates that GLP-1RAs may also offer benefits for patients with polycystic ovary syndrome (PCOS) by reducing insulin resistance and improving metabolic health. Several studies have investigated the use of GLP-1 agonists in individuals with obesity and PCOS. One early pilot study conducted by Salamun et al. found that women with obesity and PCOS who were treated with liraglutide, a GLP-1RA, experienced higher pregnancy rates compared to those receiving standard ovulation induction treatment alone [12]. The researchers suggest that liraglutide may help address insulin resistance and promote regular menstrual cycles in patients with PCOS, due to its weight-reducing and insulin-sensitizing effects. However, more research is necessary before GLP-1 agonists can be deemed effective for treating infertility and other metabolic disorders associated with PCOS.

Metabolic Benefits of GLP-1R Agonists

GLP-1 agonists have beneficial metabolic effects that enhance glucose regulation in individuals with PCOS. Animal studies indicate that these agonists help reduce calorie intake, which is a key factor contributing to the weight loss associated with their use [1,13]. GLP-1 agonists are effective for inducing weight loss in women with polycystic ovary syndrome. These medications may function by suppressing appetite and promoting energy expenditure [14]. Clinical trials have demonstrated that treatment with GLP-1 receptor agonists leads to a significant reduction in body weight and improvements in body composition, including a decrease in visceral fat mass. Such changes can enhance the metabolic profile of individuals with PCOS. The mechanisms behind GLP-1 agonists likely involve increased glucose utilization in peripheral tissues, changes in lipid distribution, and reduced glucose production by the liver. Subgroup analyses indicate that these medications effectively lower HbA1c levels, fasting plasma glucose, and triglyceride levels while increasing HDL cholesterol. These findings have been demonstrated in clinical trials [15]. These treatments lead to better glycemic control, including improved insulin sensitivity and enhanced lipid profiles [16].

Additionally, GLP-1 agonists may positively influence some fertility parameters, such as the regularity of menstrual cycles and ovulation rates [13,14,17]. Together, these changes highlight the therapeutic potential of this drug class in addressing PCOS and its related metabolic and reproductive disorders. Patients with polycystic ovary syndrome (PCOS) exhibit several characteristics, such as insulin resistance, dyslipidemia, and abdominal obesity. These features suggest that they can greatly benefit from weight loss, especially when combined with the direct metabolic effects of GLP-1 agonists [2]. GLP-1 agonists promote weight loss, improve blood sugar levels, and enhance the lipid profile, addressing many of the metabolic issues associated with polycystic ovary syndrome (PCOS). Research indicates that these medications effectively prevent insulin resistance and improve metabolic risk factors in women with this condition. Therefore, due to their various mechanisms of action, GLP-1 agonists represent a promising new treatment for enhancing metabolic health in individuals with PCOS.

Hormonal Regulation of GLP-1R Agonists

GLP-1 receptor agonists effectively suppress glucagon secretion and lower hepatic glucose production, which are essential mechanisms for enhancing insulin sensitivity in women with PCOS [18]. This reduces circulating insulin levels, countering hyperinsulinemia, a key feature of PCOS associated with androgen excess. By lowering insulin, GLP-1 agonists help reduce hyperandrogenism, addressing both metabolic and reproductive issues [2]. Research, including a meta-analysis conducted by Zhang et al., has shown that women with polycystic ovary syndrome (PCOS) experience a significant decrease in testosterone levels when treated with GLP-1 receptor agonists [19]. This reduction in androgens suggests that these treatments may help alleviate hyperandrogenic symptoms commonly associated with PCOS, such as hirsutism, acne, and irregular menstrual cycles. The mechanisms underlying these effects are thought to involve complex interactions between pancreatic hormones, ovarian and adrenal glands, and the pituitary gland. While promising, the mechanisms by which GLP-1 agonists influence insulin signaling and androgen reduction are not fully understood. Future research should explore inter-organ hormonal communication to enhance treatment protocols and identify patient subgroups that could gain the most from this therapy.

Effect of GLP-1R Agonists on Inflammation

Low-grade chronic inflammation is a common feature in women with PCOS and plays a role in worsening both insulin resistance and hyperandrogenism [20]. Recent research has demonstrated that GLP-1 agonists possess anti-inflammatory properties in the context of PCOS by inhibiting the production of the cytokines IL-6 and TNF-α (13). The study by Kahal et al, investigating the effects of liraglutide treatment on atherothrombotic risk, involved 19 obese women with PCOS and a control group of 17 individuals. After six months, the results showed that liraglutide led to an average weight loss of 3% to 4%. Additionally, there was a notable reduction in markers associated with atherothrombosis, including inflammation, endothelial function, and clotting factors [21]. GLP-1 agonists reduce the number of macrophages in adipose tissue due to inflammation. This reduction likely helps decrease systemic inflammation, which could benefit metabolic and reproductive performance when using GLP-1 agonist therapy. By further exploring the inflammatory pathways influenced by GLP-1 signaling, researchers will gain a better understanding of how these agents impact the underlying pathology of PCOS.

GLP-1 Agonists comparison with the standard treatment of PCOS: Metformin

In comparison to Metformin, GLP-1 receptor agonists like dulaglutide show superior anti-androgenic effects and positive impacts on ovarian dysfunction in models relevant to polycystic ovary syndrome (PCOS). Additionally, dulaglutide is well-tolerated and does not carry the same risk of pancreatitis that affects other GLP-1 agonists. It also improves insulin sensitivity like Metformin (5). A trial involving 30 women compared high-dose liraglutide to metformin plus low-dose liraglutide for weight loss over 12 weeks. Both treatments resulted in significant weight loss (-6.3 ± 3.7 kg for monotherapy vs. -3.6 ± 2.5 kg for combined therapy) and improved OGTT outcomes. Liraglutide alone showed greater reductions in BMI and waist circumference, while combined therapy significantly decreased total testosterone and led to less nausea [22]. In a trial with 32 obese women with PCOS, those treated with liraglutide showed

greater weight loss than those on metformin, particularly in newly diagnosed PCOS patients. The mean BMI reduced by 2.13 kg/m² for liraglutide compared to 0.62 kg/m² for metformin [23].

In conclusion, GLP-1 agonists demonstrate a superior impact compared to metformin in improving the reproductive health of PCOS patients, although they carry a slightly increased risk of gastrointestinal side effects.

Future Directions and Research Gaps

Mechanistic insights into the role of GLP-1 in ovarian function and its interaction with other agents, such as metformin, warrant further investigation [14]. Currently, there is a lack of long-term data on menstrual cyclicity, metabolic changes, and reproductive safety concerning GLP-1 agonists. Therefore, extended follow-up studies are essential [18]. Additionally, pharmacogenomics could help predict therapeutic responses across different PCOS phenotypes, which would guide applications in precision medicine [1,24].

2. Conclusions

Polycystic Ovary Syndrome (PCOS) is an endocrine disorder that affects women of reproductive age. It is characterized by infertility and metabolic issues, such as insulin resistance, which impacts up to 70% of those diagnosed with the condition. The studies outlined in this article indicate that PCOS involves a complex pathologic mechanism, with significant metabolic changes being a key factor. This condition leads to hormonal imbalances, increased testosterone levels, and associated health risks, including cardiovascular disease and dyslipidemia. Current treatments for PCOS mainly include lifestyle modifications, metformin, and hormonal therapies. However, these methods may have limitations, such as poor adherence and potential side effects. Over the years, treatments targeting the metabolic aspects of PCOS have been developed. These promising results have led to significant interest in using GLP-1-based medications in managing type 2 diabetes.

Recently, glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as a promising treatment option for polycystic ovary syndrome (PCOS). Originally developed for type 2 diabetes, these medications improve insulin sensitivity, promote weight loss, and address the metabolic disturbances associated with PCOS. Research indicates that GLP-1 agonists, such as liraglutide, can enhance pregnancy rates and overall reproductive outcomes in overweight or obese women with PCOS. By improving metabolic health and addressing insulin resistance, GLP-1 agonists offer a valuable therapeutic approach. However, further studies are necessary to confirm their effectiveness in the treatment of PCOS.

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