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Benefits of administering GLP-1 analogs to patients with polycystic ovary syndrome, considering their effect on adipose tissue metabolism

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ABSTRACT

Mammals have 2 primary types of adipose tissue: brown adipose tissue (BAT) and white adipose tissue (WAT). White adipose tissue, one of the largest organs, spans the entire body and persists throughout an individual's life, with the highest concentrations found in the abdominal cavity or subcutaneously. In obese individuals, the amount of WAT can reach up to 70% of total body weight. Today, glucagon-like peptide-1 (GLP-1) analogs have gained popularity in the treatment of obesity, insulin resistance, and related metabolic disorders. Patients using glucagon-like peptide-1 receptor agonists (GLP-1RAs) have improved lipid profiles, reduced visceral fat accumulation, and improved glucose tolerance. Polycystic ovarian syndrome (PCOS) is a disorder strongly associated with insulin resistance and obesity. It is the most common heterogeneous endocrine disorder, affecting an estimated 1 in 5 women of reproductive age. The introduction of GLP-1 analog treatment in women with PCOS could help to manage the disease, improve the quality of life of PCOS patients, increase their chances of conception, and maintain pregnancy until delivery. This review presents the latest reports on the use of GLP-1RAs and the treatment of PCOS.

Keywords: glucagon-like peptide-1 agonists; adipose tissue; obesity; polycystic ovary syndrome.

INTRODUCTION

Adipose tissue characterization

Mammals have 2 primary types of adipose tissue: brown adipose tissue (BAT) and white adipose tissue (WAT), which can be distinguished by their macroscopic characteristics. White adipocytes are generally larger than brown adipocytes and contain a single substantial lipid droplet within the cytoplasm. In contrast, brown adipocytes contain numerous smaller lipid droplets. In addition, BAT cells contain an increased number of mitochondria, a feature consistent with their primary role in thermogenesis [1]. Brown adipose tissue positively influences lipid and carbohydrate metabolism by removing glucose and lipids from the bloodstream, thereby reducing the need for insulin secretion from pancreatic beta cells [2].

In contrast to BAT, the primary function of WAT is to store energy in the form of triglycerides (TAG). Therefore, WAT is able to store energy as TAG and release it during periods of increased energy demand by breaking down TAG into fatty acids. In addition, WAT assumes an endocrine role by secreting adiponectins such as adiponectin or leptin [3, 4, 5].

There are also differences in the location and lifespan of WAT and BAT. White adipose tissue is found throughout the body and persists throughout the lifespan, with the highest concentrations found in the abdominal cavity or subcutaneously [6]. Brown adipose tissue, on the other hand, occurs primarily in infants and is localized primarily in the interlobular space and surrounding muscles and blood vessels until the first decade of life. In adulthood, BAT nearly disappears within 6 decades. It remains present in limited areas: around the kidneys, adrenal glands, aorta, neck, and mediastinum [7, 8].

In addition, a third type of adipose tissue has been identified: beige adipose tissue, an intermediate between BAT and WAT. This tissue is not confined to distinct deposits like BAT but is intermingled with WAT [2, 9].

Excessive growth of adipose tissue leads not only to the formation of subcutaneous fat deposits but also to visceral fat depots and fat accumulation in ectopic tissues, resulting in life-threatening obesity [10]. This impairs the endocrine function of adipose tissue and triggers chronic inflammation (mainly mediated by WAT), which initiates a series of pro- and anti-inflammatory pathways leading to adipocyte dysfunction. This dysfunction can subsequently lead to insulin resistance [11, 12]. Obesity-related insulin resistance is associated with a wide range of disorders, including dyslipidemia, non-alcoholic fatty liver disease (NAFLD), hypertension [13], cardiovascular disease, and stroke [14]. Treatment of obesity is essential to maintain health and minimize the consequences of obesity-related diseases. Patient awareness is critical in this process. Depending on the severity of obesity, treatment includes lifestyle changes (dietary modification, nutritional therapy, physical activity), pharmacotherapy (orlistat, a gastrointestinal lipase inhibitor that blocks the absorption of dietary fat [15]; sibutramine, a monoamine reuptake inhibitor [16]; phentermine/topiramate, an appetite suppressant (pharmacologically

related to amphetamine) [17]; naltrexone-bupropion, which interferes with the reward pathway resulting in reduced food craving [18]), and even bariatric surgery [19, 20]. Treatment of insulin resistance very often starts with weight loss but additional medications (such as metformin, a biguanide with glucose-lowering effects [21]; sodium-glucose cotransporter 2 (SGLT2) inhibitors, which block glucose at SGLT2 receptors in the proximal tubules of the kidney and inhibit urinary glucose reabsorption [22]) are needed; thiazolidinediones, insulin sensitizers [23], and dipeptidyl peptidase-4 – DPP-4 inhibitors, which inhibit the breakdown of incretins [24]), depending on the severity of the disease [20]. Nowadays, glucagon-like peptide-1 (GLP-1) analogs are used in the treatment of obesity and insulin resistance due to the presence of GLP-1 receptors in mature adipocytes and stromal-vascular cells, with a notable dominance in the latter [25]. The efficacy of GLP-1 in these roles is attributed to its ability to modulate the expression of glucose transporters 1 and 4 in adipocytes [26], together with its dose-dependent lipolytic effects mediated by adenylyl cyclase activity [15, 17]. The efficacy and presumed safety of the use of glucagon-like peptide-1 receptor agonists (GLP-1RAs), together with their tolerability, have made them highly prescribed drugs, not only for the treatment of life-threatening diseases but also as slimming agents in healthy individuals [27, 28]. However, it should be noted that the long-term side effects of the use of GLP-1 analogs are still not determined and recent studies suggest their involvement in the pathophysiology of pancreatitis, increased risk of medullary thyroid cancer, and progression of diabetic retinopathy [29, 30, 31].

The action of glucagon-like peptide-1

Glucagon-like peptide-1 is a peptide hormone of the incretin family consisting of 30–31 amino acids. The discovery of GLP-1 and its properties redirected the treatment of diabetes [32]. Endogenous GLP-1 actions include increasing postprandial insulin secretion, controlling gastric motility [33], and decreasing postprandial glucagon release [34, 35, 36, 37]. The peptide increases muscle insulin sensitivity, promotes lipolysis, and decreases lipogenesis. The same effects are obtained when GLP-1 analogs are administered. Thus, GLP-1 analogs are not only used in the treatment of diabetes but are gaining popularity in the treatment of obesity, insulin resistance, and related metabolic disorders, as well as in the prevention of cardiovascular disease. Receptors for GLP-1 are found in various tissues of the human body (including the pancreas, gastrointestinal tract, heart, lung, kidney, adipose tissue, and brain) [15, 21, 22, 23]. Looking at adipose tissue, GLP-1 receptor expression is most pronounced in WAT of morbidly obese patients with insulin resistance and shows a positive correlation with the homeostasis model assessment of insulin resistance (HOMA-IR) [25]. Given that individuals with insulin resistance and diabetes may have reduced circulating GLP-1 levels [38, 39, 40]. This correlation may suggest a compensatory mechanism to enhance the interaction of GLP-1 with adipose tissue. This mechanism may explain the increased efficacy of GLP-1 analogs in the treatment of obesity [25].

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS ACTION ON ADIPOSE TISSUE

Glucagon-like peptide-1 analogs are a relatively new group of drugs, synthetic counterparts of human GLP-1, typically administered by subcutaneous injection [25, 26]. Based on their duration of action, they can be classified into short-acting, including exenatide and lixisenatide, and long-acting: liraglutide, dulaglutide, albiglutide, and semaglutide [41] – Table 1. Glucagon-like peptide-1 receptor analogs, such as liraglutide and semaglutide, have emerged as breakthrough therapies, not only in reducing blood glucose levels in patients with diabetes but also in treating obesity [42]. Liraglutide, administered subcutaneously at a dose of 3 mg, has been shown to reduce appetite, alter taste preferences, and decrease body fat stores, including total body fat, trunk fat, upper body fat, and lower body fat [43]. A meta-analysis conducted by Berg et al. also demonstrated reduced low-density lipoprotein (LDL) and TAG levels after GLP-1 analog use in diabetic patients [44]. In rats, liraglutide increases levels of glyoxalase 1 (GLO-1), an enzyme associated with impaired capillarity and insulin resistance in obese individuals, by decreasing its activity in adipose tissue. Liraglutide also contributes to increased angiogenic compounds and improved insulin sensitivity [45].

Tirzepatide, a GLP-1 and glucose-dependent insulinotropic peptide (GIP) receptor agonist, appears to be a revolutionary drug for the treatment of obesity in diabetic patients. The drug produces substantial and sustained reductions in body weight [46], shows superior and clinically significant reductions in hemoglobin A1c (HbA1c) compared to glargine (an extended-release human insulin analog) [31], improves pancreatic beta cell function [47], and demonstrates safety by not posing a risk of hypoglycemia during use [48, 49, 50]. Samms et al. also note that the drug reduces systemic levels of branched-chain amino acids and ketoacids by increasing their catabolism in mouse BAT [51]. These amino acids are associated with insulin resistance, and reducing their levels results in improved glycemic control and decreased body weight [36, 37, 38].

In addition to inducing fat reduction, semaglutide reduces the expression of endoplasmic reticulum stress genes and subsequently reduces inflammation by reducing the expression of pro-inflammatory genes such as activating transcription factor-4 (ATF4) and cytosine-cytosine-adenosine-thymidine (CCAAT) enhancer-binding protein (C/EBP) homologous protein (CHOP). In epididymal white adipose tissue (eWAT), semaglutide treatment reduces growth arrest and deoxyribonucleic acid (DNA)-damage inducible gene 45, interleukin 6 (IL-6), interleukin 1 beta (IL-1β), monocyte chemoattractant protein 1 (MCP 1), and tumor necrosis factor alpha (TNF-α), particularly in subjects on a high-fat diet [52]. Notably, histological images of adipocytes after semaglutide treatment show decreased macrophage infiltration and hypotrophy of adipocytes.

A recent study by Zhu and Chen examined the proteomics of eWAT in obese mice and suggested that semaglutide treatment may positively affect adipose tissue by regulating lipid uptake, storage, and lipolysis in WAT [53]. Semaglutide-treated mice

TABLE 1. Glucagon-like peptide-1 analogs list with properties and the indication to use

Name	Half-life	Dosage	Approved date	Approved indication
Exenatide	2.4 h or extended-release, peak at 840 h	twice-daily injection or once-weekly injection	Apr, 2005 (FDA)/ Jan, 2012 (FDA)	type 2 diabetes mellitus treatment
Liraglutide	13 h	once-daily injection	Jan, 2010 (FDA)	type 2 diabetes mellitus treatment and chronic weight management to reduce the risk of major adverse cardiovascular events
Albiglutide	120 h	once-weekly injection	Apr, 2014 (FDA)	type 2 diabetes mellitus treatment
Dulaglutide	90 h	once-weekly injection	Sep, 2014 (FDA)	type 2 diabetes mellitus treatment
Lixisenatide	3–4 h	once-daily injection	Jul, 2016 (FDA)	type 2 diabetes mellitus treatment
Beinaglutide	1–2 min	3 times – daily injection	Dec, 2016 (CFDA)	type 2 diabetes mellitus treatment
Semaglutide	160 h/7 days	once-weekly injection/ once-daily oral	Dec, 2017 (FDA)/ Sep, 2019	type 2 diabetes mellitus treatment, chronic weight management, to reduce the risk of major adverse cardiovascular events
Polyethylene glycol loxenatide	80 h	once-weekly injection	May, 2019 (CFDA)	type 2 diabetes mellitus treatment
Tirzepatide	5 days	once-weekly injection	May, 2022 (CFDA)	type 2 diabetes mellitus treatment (used off-label for obesity treatment)

showed decreased expression of proteins associated with lipid metabolism, such as lipoprotein lipase (LPL), monoacylglycerol lipase (MGLL), aquaporin-7 (AQP-7), pyruvate dehydrogenase (acetyl-transferring) kinase isozyme 4 (PDK4), angiopoietin-related protein 4 (ANGPTL4), platelet glycoprotein 4 (CD36), fatty acid-binding protein 5 (FABP5), long-chain fatty acid CoA ligase 1 (ACSL), perilipin-2 (PLIN2), and peroxisomal acyl coenzyme A oxidase 3 (ACOX3). This reduction was associated with reduced visceral fat accumulation, improved blood lipid levels, and improved glucose tolerance. These findings suggest that semaglutide treatment may favorably affect adipose tissue by regulating lipid-related processes (Fig. 1).

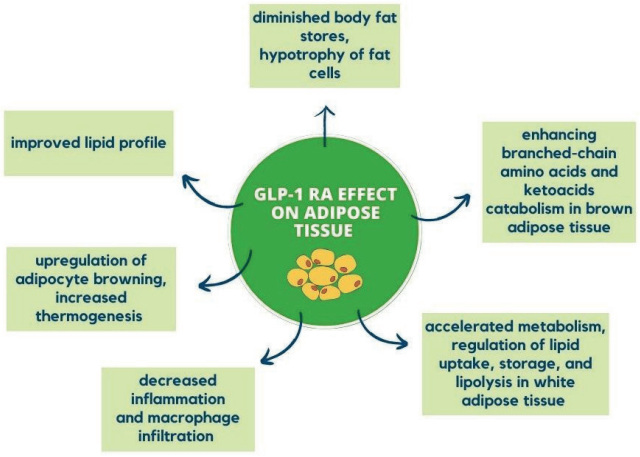


FIGURE 1. The action of glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) on adipose tissue

Endogenous GLP-1 affects BAT metabolism by regulating thermogenesis [54, 55, 56]. Comparable effects may be achieved by administration of GLP-1 analogs. In particular, semaglutide shows beneficial effects on adipocyte browning as reflected by increased expression of peroxisome proliferator-activated receptor (PPAR) alpha, PPAR gamma, and fibronectin type III domain-containing protein 5 (FNDC5), especially in the high-fat diet group. In addition, semaglutide increases mitochondrial biogenesis through increased messenger ribonucleic acid (mRNA) expression of peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α), nuclear respiratory factor 1 (NRF-1), and mitochondrial transcription factor A (TFAM). This leads to improved thermogenesis as indicated by upregulation of β3-adrenergic receptor (β3-AR), positive regulatory domain containing 16 (PRDM16), and uncoupling protein-1 (UCP1).

The glucagon-like peptide-1 receptor agonist exenatide also activates sirtuin 1 (SIRT1), leading to the deacetylation of forkhead box O1 (FOXO1), which in turn activates adipose triglyceride lipase (ATGL). This cascade causes changes in WAT, accelerating its metabolism and promoting weight loss [42, 43].

GLUCAGON-LIKE PEPTIDE-1 ANALOGS AND POLYCYSTIC OVARY SYNDROME

The ovaries, which play a key role in fertility, are composed of 3 parts: the hilum, cortex, and medulla [57]. The cortex consists of the outer and inner zones in which the ovarian follicles are embedded [58]. As the primary functional units of the ovaries, the main purpose of the follicles is ovulation, a process regulated by the hormones: follicular stimulating hormone (FSH) and luteinizing hormone (LH) [59, 60, 61, 62, 63].

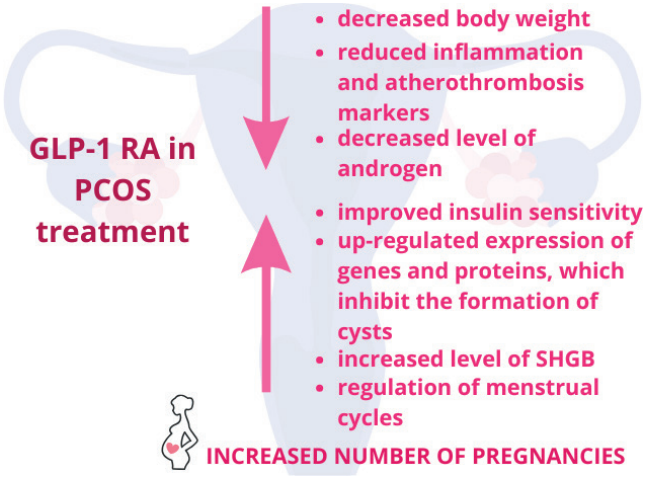
Polycystic ovary syndrome (PCOS) is the most common heterogeneous endocrine disorder, affecting an estimated 1 in 5 women of reproductive age [47, 48]. It is primarily associated

with endocrine disruption and excess androgens, resulting in the appearance of multiple cysts in the ovarian structure, abnormal menstrual cycles, and lack of ovulation [49, 50]. Studies also suggest a strong association between the development and severity of PCOS with environmental and epigenetic factors [64, 65, 66]. Polycystic ovary syndrome is strongly associated with insulin resistance (in both obese and lean individuals) and obesity (80% of patients) [48, 52, 53]. The increasing amount of insulin secreted stimulates androgen production in the ovaries, exacerbating hyperandrogenism [67, 68]. Polycystic ovary syndrome adversely affects quality of life through deterioration of mental status and mood, and increased risk of cardiovascular events. It may even lead to the development of ovarian neoplasms over time [51, 55].

The increased insulin sensitivity and weight loss associated with the use of GLP-1 analogs and the widespread expression of GLP-1 receptors (including the hypothalamic-pituitary-gonadal axis) have expanded the use of these drugs to the treatment of obesity, insulin resistance, and related metabolic disorders, the prevention of cardiovascular disease, and the management of PCOS.

Animal studies using liraglutide have shown that the drug affects ovarian follicle development by regulating the ovarian phosphoinositide 3-kinase (PI3K) / protein kinase B (PKB/AKT) pathway and the phosphorylation of FOXO1 proteins [69]. Research on dulaglutide in rats has shown that it can reduce androgen levels as a result of the upregulation of sex hormone binding globulin (SHBG) in rat serum. In addition, it upregulates the expression of 3β-hydroxysteroid dehydrogenase (3βHSD), cytochrome P450 family 19 subfamily a member 1 (CYP19α1), and steroidogenic acute regulatory protein (StAR) genes and proteins, which inhibits the formation of cysts and pus in the ovaries of PCOS rats [70]. Similar effects have been observed in exenatide studies, with increased numbers of cystic follicles, and reduced corpus luteum [71], and restoration of regular menstrual cycles [72]. Dehydroepiandrosterone-induced PCOS mice treated with liraglutide were also able to restore normal menstrual cycles [73]. However, in a study of rats treated with a dihydrotestosterone (DHT) pellet, no improvement in menstrual cycle regularity was observed [74, 75, 76, 77, 78, 79, 80, 81, 82].

In clinical trials, treatment with GLP-1 analogs leads to significant weight loss in patients with PCOS [62, 63, 64, 65, 66, 67, 68]. Liraglutide, like exenatide, can significantly reduce inflammation and atherothrombosis markers such as inflammation, endothelial function, and coagulation [56, 69, 70]. It has also been shown to significantly reduce serum endothelial adhesion markers: soluble platelet selectin (sP-selectin), soluble intercellular adhesion molecule (sICAM), soluble vascular cell adhesion molecule (sVCAM), and clot lysis area [83, 84, 85, 86, 87] (Fig. 2).



SHBG – sex hormone-binding globulin

FIGURE 2. The influence of glucagon-like peptide-1 receptor agonists (GLP-1RAs) administration on polycystic ovary syndrome (PCOS) management

A reduction in adipose tissue deposition decreases the inflammatory status and the concentration of circulating cytokines. This results in the inhibition of cyst formation, which, together with decreased androgen levels and increased SHBG levels, leads to the regulation of menstrual cycles and the increased number of pregnancies (Fig. 2).

Liraglutide improved ovarian function, decreased testosterone levels, increased SHBG levels, decreased ovarian size, and decreased mean body weight [71, 72]. Similar effects were seen in patients treated with exenatide [66, 69, 73]. Glucagon-like peptide-1 analogs may also increase the number of normal menstrual cycles [66, 71, 74] and increase the number of pregnancies in treated women with PCOS, especially in patients using liraglutide-metformin combination therapy [65, 71, 73].

CONCLUSIONS

The wide range of applications of GLP-1 analogs is the reason for their growing interest among clinicians of many disciplines. The treatment of type 2 diabetes is undoubtedly one of the most important applications of the drugs but the actions of GLP-1 analogs, including increasing insulin sensitivity, decreasing circulating insulin levels, anorexiogenic effect, and weight loss, make the drug an important tool in the fight against obesity and related metabolic disorders. Glucagon-like peptide-1 analogs positively affect adipose tissue by regulating lipid uptake, storage, and lipolysis in WAT, accelerating its metabolism and reducing inflammation. Patients using GLP-1RAs have improved lipid profiles, reduced visceral fat accumulation, and improved glucose tolerance. Glucagon-like peptide-1 analogs also have beneficial effects on adipocyte browning and reduce systemic levels of molecules associated with insulin resistance by increasing their catabolism in BAT. The introduction of GLP-1 analog treatment in women with PCOS could help manage the disease, improve the quality of life of PCOS patients, and increase their chances of conceiving and carrying a pregnancy to term. However, because of the limited

research on the effects of GLP-1 analogs on pregnancy and the developing fetus, it is important to instruct the patient to use birth control during treatment and to discontinue treatment prior to conception.

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