GLP-1 Receptor Agonists in Polycystic Ovary Syndrome Management

Subjects: Medicine, General & Internal

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Polycystic ovary syndrome (PCOS) is the most common metabolic and hormonal disorder in reproduction-aged women. Its pathogenesis involves multiple organ systems and is tightly associated with a higher predisposition and prevalence of abdominal obesity and insulin resistance. Profound weight loss effects in diabetic and non-diabetic patients gave birth to the idea that GLP-1 receptor agonists (GLP-1RAs) could be used in a subgroup of women with PCOS.

GLP-1 receptor | polycystic ovary syndrome | management

1. The Efficacy of GLP-1 Receptor Agonists in Weight Management in Polycystic Ovary Syndrome

In 2014, the United States Food and Drug Administration (FDA) approved liraglutide as the first GLP-1 receptor agonist (GLP-1RA) that can be used for obesity management in patients without diabetes [1]. In 2021, semaglutide followed with indications in obese patients (BMI above 30 kg/m^2) or overweight patients (BMI above 27 kg/m^2) with at least one adipose-based chronic diseases (ABCD) [2]. GLP-1RAs alone or combined with metformin have been investigated in several small studies with overweight/obese PCOS women [3]. **Table 1** summarizes the clinical studies that measured the weight-reducing effects of GLP-1RAs in PCOS patients as one of their outcomes.

Additional insight was provided by a network meta-analysis including 23 studies and 951 women, which compared the effectiveness of liraglutide, orlistat, and metformin in promoting weight loss in PCOS women. Liraglutide monotherapy was superior in reducing body weight and waist circumference. Furthermore, its efficacy was the highest at the daily dose of 3 mg [4].

Table 1. Clinical studies that measured the weight loss effects of GLP-1RAs in PCOS.

Population Studied	Study Type	Duration	Study Arms	Weight Loss	Other Remarks	Ref
40 obese nondiabetic women with PCOS who had lost <5% body weight during pretreatment with metformin	Open-label, prospective study	12 weeks	Metformin 1000 mg BID	−1.2 ± 1.4 kg	WC also decreased by 5.5 ± 3.8 cm in the combination arm compared with 3.2 ± 2.9 cm in liraglutide and 1.6 ± 2.9 cm in the	[5]
			liraglutide 1.2 mg QD s.c.	−3.8 ± 3.7		

Population Studied	Study Type	Duration	Study Arms	Weight Loss	Other Remarks	Ref
				kg	metformin arm. The majority of patients who achieved at least 5% of weight reduction were on combination therapy or liraglutide monotherapy.	
			metformin 1000 mg BID and liraglutide 1.2 mg QD s.c	−6.5 ± 2.8 kg		
32 obese women with newly diagnosed PCOS	Open-label, prospective study	12 weeks	Metformin 1000 mg BID	−2.3 kg	Comparable results were found for the reduction of BMI, WC and whole-body fat mass. However, in a subgroup of patients with the combination of extreme obesity and insulin resistance, the patients achieved better results with liraglutide compared to metformin.	[6]
			Liraglutide 1.2 mg QD s.c.	−3.0 kg		
84 overweight/obese women with PCOS	Observational study	a minumum of 4 weeks; a mean duration of treatment was 27.8 weeks	Starting dose was 0.6 mg liraglutide given s.c. QD. If the weight was not reduced, the dose was increased to 1.2 mg and if necessary to 1.8 mg.	−9.0 kg	81.7% of patients achieved beyond 5% weight loss, and 32.9% of patients achieved more than 10% weight loss.	[7]
72 women with PCOS, with a BMI > 25 kg/m^2 and/or insulin resistance	Prospective, double-blind, placebo-controlled, randomized clinical trial	26 weeks	Placebo	0.2 kg	Body weight reduction of more than 5% was achieved in 55% and 14% of participants in the liraglutide and placebo groups, respectively. In addition to liver fat content, VAT and SAT were reduced	[8]
			liraglutide 1.8 mg QD s.c	−5.2 kg		

Population Studied	Study Type	Duration	Study Arms	Weight Loss	Other Remarks	Ref
					by 18.6% and 10.0%, respectively.	
44 obese women with PCOS	Open-label, prospective, randomized control trial	12 weeks	Liraglutide 1.2 mg QD s.c.	−3.8 ± 3.5 kg	59.1% of patients in the cobination groups vs. 42.9% of patients in the liraglutide-only group achieved beyond 5% weight reduction.	[9]
			metformin 1000 mg BID and liraglutide 1.2 mg QD s.c.	−6.2 ± 2.4 kg		
31 obese patients with PCOS	Retrospective study	6 months	Metformin 500 or 1000 mg daily	−4.9 kg	Liraglutide was superior in the analysis of the number of patients that achieved 5% or 10% weight loss.	[10]
			Liraglutide doses of 1.8 mg and 3.0 mg or semaglutide dosing up to 1 mg	−9.1 kg		
50 overweight/obese PCOS women	Open-label prospective, randomized, clinical trial	12 weeks	Metformin 500 mg TID	−2.1 ± 3.0 kg	WC decreased by 4.63 ± 4.4 cm in combination group compared with 1.72 ± 3.07 cm in the metformin-only group.	[11]
			metformin 500 mg TID, exenatide 2 mg QW	−3.8 ± 2.4 kg		
60 overweight oligoovulatory women with PCOS	Open-label prospective, randomized, clinical trial	24 weeks	Metformin 1000 mg BID	−1.6 ± 0.2 kg	Combination therapy was more efficient compared to to exenatide or metformin in reducing abdominal fat.	[12]
			exenatide 10 mcg BID	−3.2 ± 0.1 kg		
			metformin 1000 mg BID and exenatide 10 mcg BID	−6.0 ± 0.5 kg		
19 obese women with PCOS	Open label, prospective	6 months	Liraglutide 1.8 mg QD	−3.0 ± 4.2 kg	/	[13]
45 obese PCOS women	Open-label, prospective, randomized clinical trial	12 weeks	Metformin 1000 mg BID	−0.2 ± 1.8 kg	Liraglutide also resulted in significant decrease in VAT area and was superior in reducing WC.	[14]
			roflumilast 500 mcg QD	−2.1 ± 2.0		

Population Studied	Study Type	Duration	Study Arms	Weight Loss	Other Remarks	Ref
				kg		
			liraglutide 1.2 mg QD	−3.1 ± 3.5 kg		
30 obese PCOS women	Open-label prospective randomized clinical trial	12 weeks	Metformin 1000 mg BID and liraglutide 1.2 mg QD	−3.6 ± 2.5 kg	WC reduction in liraglutide arm was greater than in combination.	[15]
			liraglutide 3.0 mg QD	−6.3 ± 3.7 kg		
28 infertile obese PCOS patients	Open-label prospective randomized clinical trial	12 weeks	Metformin 1000 mg BID	−7.0 ± 6.0 kg	Weight reduction beyond 5% was seen in 69.2% of patients in the combination group and 57.1% of patients in the metformin-only group. Significant and similar decreases in WC, VAT area, and volume were noticed between groups.	[16]
			metformin 1000 mg BID combined with liraglutide 1.2 mg QD	−7.5 ± 3.9 kg		
176 overweight/obese women with PCOS	Open-label prospective, randomized clinical trial	24 weeks	Metformin 1000 mg BID	−2.3 ± 0.6 kg	47% of patients achieved beyond 5% weight loss with exenatide therapy in the first 12 weeks, but no subject demonstrated similar weight loss with MET therapy. The decrease in WC was more significant in patients on exenatide than those in patients on metformin. Exenatide therapy resulted in	[17]
			exenatide 10 µg BID (first 12 weeks), metformin 1000 mg BID (second 12 weeks)	−4.3 ± 1.3 kg		

Population Studied	Study Type	Duration	Study Arms	Weight Loss	Other Remarks	Ref
					significant decreases in abdominal fat.	
30 overweight/obese anovulatory women with all 3 Rotterdam criteria	Open label, prospective study	16 weeks	exenatide 5 mcg BD for 4 weeks then 10 mcg BD for 12 weeks	−3.2 kg	There was no effect on WC but there was a reduction in hip circumference.	[18]
32 overweight/obese PCOS patients	Prospective study	12 weeks	the initial dose of exenatide 5 μg BD was increased to 10 μg BD after 1 month	−6.0 kg	After exenatide treatment, the body adipose distribution—related indexes, including body fat content, WC, and hipline circumference, decreased.	[19]
119 nondiabetic obese women with PCOS	Single-blinded, randomized controlled trial	24 weeks	once-weekly 2 mg exenatide (EQW)	−4.1 kg	The combination of exenatide and dapagliflozin resulted in superior weight and total body fat reductions than either therapy individually.	[20]
			dapagliflozin 10 mg daily (DAPA)	−1.4 kg		
			coadministered EQW/DAPA	−6.0 kg		
			DAPA/extended-release (ER) metformin 2000 mg daily (DAPA/MET)	−1.8 kg		
			phentermine 7.5 mg/topiramate extended release 46 mg ER daily	−9.0 kg		
25 obese women with PCOS	Randomized single-blind, pilot study	16 weeks	placebo [23]	−1.9 ± 1.5 kg	Tongue fat tissue and fat proportion significantly reduced after semaglutide vs. placebo and were assocaited with those in body weight, BMI and WC.	[21]
			semaglutide 1.0 mg [24][25][26]	−5.2 ± 4.0 kg		

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arms compared to the baseline, without significant differences between the arms [22]. Further information on the metabolic effects was provided in a study evaluating the impact of exenatide on different metabolites in women with PCOS and matched controls [19]. The three-month trial demonstrated that triglycerides, HDL, LDL, total cholesterol, and branched-chain amino acid metabolism were improved following exenatide therapy [19].

Population Studied	Study Type	Duration	Study Arms	Weight Loss	Other Remarks	Ref
182 women with PCOS	Randomized controlled trial	12 weeks	metformin 1000 mg BID [27]	−3.6 kg	There was a significant decrease in WC in both treatment groups, and exenatide group was better in changes of WC than metformin group.	[22]
			exenatide 10 µg BID [28]	−5.2 kg		

Legend: WC—waist circumference, VAT—visceral adipose tissue, SAT—subcutaneous adipose tissue.

Regularity in Polycystic Ovary Syndrome

Despite menstrual regularity being an important treatment outcome in PCOS, the effect of GLP-1 levels or treatment with GLP-1RAs remains insufficiently studied. The first study to investigate the impact of GLP-1RA on the menstrual cyclicity randomized 42 oligo-ovulatory and overweight PCOS women to exenatide, metformin, or both. After 24 weeks, a significant improvement in the ovulation rate was demonstrated in all the groups, with the highest rate in the combination group and the lowest in the metformin-only group. Furthermore, the improvement in menstrual regularity was significantly correlated with a reduction in body weight, suggesting weight loss to be the primary driving factor behind the reproductive improvement [12]. A similar correlation between the change in menstrual frequency and BMI was found in a 26-week randomized, placebo-controlled trial that explored the effect of liraglutide 1.8 mg daily on ovarian function in 72 women with PCOS [29]. The bleeding ratio of 0.87 or above (calculated by the number of menstrual bleedings divided by the number of months in the study period) was achieved in 62% of women in the liraglutide group compared with 28% in the placebo group [29]. However, several additional studies with liraglutide in PCOS found unaltered menstrual rate despite reductions in body weight [5][6][14] and insulin resistance [13]. Potential explanations might include small sample sizes, short duration, and the low liraglutide dose [30].

4. The Effects of GLP-1 Receptor Agonists on Pregnancy Rate in Polycystic Ovary Syndrome

There were two studies that addressed pregnancy rates in women with PCOS after an intervention with GLP-1RAs before conception, both reporting better pregnancy outcomes after the GLP-1RA withdrawal [16][17]. The first study included 176 overweight or obese women with PCOS and investigated the natural pregnancy rate in the following 12 weeks after a 12-week treatment with exenatide [17]. The study participants were randomized to receive either exenatide 10 mcg BID or metformin 1000 mg BID for the first 12 weeks, followed by metformin only for the second 12 weeks in which the natural pregnancy rate was tracked. In comparison to the metformin group, the participants receiving exenatide had significantly improved clinical variables after the first 12 weeks, including weight, total percentage of fat, HOMA-IR, and menstrual frequency. The study's main outcome, the natural pregnancy rate following pre-treatment, was significantly higher in the exenatide group compared to the metformin group (43.6% versus 18.70%, respectively). Although the study was not designed to investigate the underlying mechanisms of this difference in the reproductive outcome, the authors proposed weight loss to most likely be the main contributor

to the improved fertility [17]. The second study included 28 obese women with PCOS and explored intervention with low-dose liraglutide (1.2 mg QD) in combination with metformin. The combination of liraglutide and metformin was superior to metformin alone in increasing both the in vitro fertilization and cumulative (including spontaneous conception) pregnancy rates after pre-treatment in patients that were previously resistant to reproductive treatment. The pregnancy rate per embryo transfer was 85.7% in the combination group, compared to 28.6% in the metformin alone group. The cumulative pregnancy rate in 12 months was 69% in the combination compared to 36% in the metformin group. Those results could provide an additional perspective in understanding the direct reproductive effects of GLP-1RAs since both interventions resulted in comparable weight and visceral adipose tissue reductions, indicating other potential mechanisms of action beyond weight loss [16]. In addition, a case report of a 26-year-old infertile and obese PCOS woman reported successful pregnancy following 2-month preconception treatment with exenatide [31].

5. The Effects of GLP-1 Receptor Agonists on Cardiovascular Outcomes in Polycystic Ovary Syndrome

PCOS is known to be linked to adverse cardiovascular risk since insulin resistance is a vital factor in its pathogenesis, importantly leading to several cardiometabolic abnormalities [32]. In comparison to age and BMI-matched healthy controls, women with PCOS have a 30% increased risk of cardiovascular disease [33]. Whether PCOS is associated with subclinical and clinical atherosclerosis, independent of risk factors that commonly accompany the disorder, is unclear [32]. In recent years, cardiovascular outcomes trials have demonstrated that GLP-1RAs can significantly reduce cardiovascular events in individuals with Type 2 diabetes mellitus, however, the majority of available studies with GLP-1RAs in PCOS did not study cardiometabolic endpoints [34][35].

The first study that was designed to assess cardiometabolic endpoints was a 6-month controlled trial, which published its results in 2015. The effect of daily liraglutide 1.8 mg on weight loss and atherothrombosis markers was evaluated in a small group of PCOS women with obesity and controls. Liraglutide treatment was associated with a significant reduction in atherothrombosis markers in both groups, including inflammation, endothelial dysfunction, and clotting [13]. Two years later, the LIPT study (Liraglutide in PCOS on Markers of Vascular Thrombosis) reported effects of the same liraglutide dose in a 26-week study in 72 overweight PCOS women on markers of thromboembolism and cardiovascular disease. The trial demonstrated significant decreases in peak thrombin concentration and increases in time to start of thrombin generation and time to peak thrombin concentration. In addition, there was an improvement in fibrinolytic activity [36]. Additional cardiovascular biomarkers were reported by this research team in this study group a year later. Liraglutide treatment reduced the levels of the cardiovascular risk biomarkers for subclinical cardiovascular disease, midregional-pro-adrenomedullin by 25%, and midregional-pro-atrial natriuretic peptide by 6% (borderline significance) compared with placebo, whereas copeptin levels did not change [37]. The LIPT study also demonstrated reductions in liver fat content, visceral adipose tissue, and the prevalence of non-alcoholic fatty liver disease [8]. Furthermore, in a 4-month study that assessed the effect 16 weeks exenatide intervention on inflammation, endothelial dysfunction, and fibrinolytic activity in 30 overweight/obese women with PCOS, the treatment showed a significant reduction in the

cardiovascular risk markers including cellular adhesion molecule 1, p-selectin as well as e-selectin, and an improvement in the C-reactive protein (CRP) [18].

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