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Incretin System: New Pharmacological Target in Obese Women with Polycystic Ovary Syndrome

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Abstract

Introduction: Obesity is highly prevalent in polycystic ovary syndrome (PCOS). It aggravates adverse features of the syndrome. Weight management by lifestyle intervention is often insufficient. We reviewed studies addressing the use of agents mediating through incretin system in obese PCOS.

Material and methods: Available relevant clinical trials were searched from PubMed.

Results: Intervention with glucagon-like peptide 1 (GLP-1) analogue liraglutide is associated with consistent body mass index (BMI) reduction in treatment-naïve obese women with PCOS and in poor responders to metformin and lifestyle modification. We recognized metformin as a well-suited combination with liraglutide. We demonstrated that liraglutide could also improve eating behavior and fertility potential in obese PCOS. Furthermore, we challenged the potential association of variability of GLP-1 receptor genotype and interindividual differences in response to liraglutide. In addition, we introduced the original concept related to the enhancement of incretin axis through phosphodiesterase 4 (PDE4). Nevertheless, we considered dipeptidyl peptidase 4 inhibitors as an alternative pharmacological intervention in metformin intolerant patients with PCOS.

Conclusion: Agents mediating through incretin system in combination with lifestyle intervention and metformin could improve treatment outcomes in obese PCOS patients. Further studies are needed to establish the benefit/risk profile achieved by these potential new treatment strategies.

Keywords: GLP-1 receptor agonist, liraglutide, DPP4 inhibitor, weight reduction, PCOS

1. Introduction

Obesity is one of a key phenotype of polycystic ovary syndrome (PCOS). The risk for excess body weight in this population is up to 2.8 higher than in women without PCOS. About 60–70% of patients are being characterized as obese or overweight [1, 2]. The amount and distribution of fat is a major contributor to expression and severity of the syndrome [3, 4]. Obese women demonstrate more severe gynecological abnormalities and clinical and biochemical hyperandrogenism than normal weight or lean women with PCOS. Insulin resistance, glucose derangements including impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM) and an increased overall cardiovascular risk are also more likely in obese PCOS [5–7]. Weight reduction is substantial for improvement of metabolic and androgen profile, reproductive function and reducing cardiovascular risk. Weight management by lifestyle intervention often remains unsatisfactory and nonsustainable. In the present chapter, we revised limited studies addressing the potential use of agents mediating through glucagon-like peptide 1 (GLP-1) in obese PCOS. We mainly focused on the available clinical trials of GLP-1 receptor agonists in this population. In addition, we challenged the original concept related to the enhancement of GLP-1-mediated action through phosphodiesterase 4 (PDE4). Nevertheless, we considered dipeptidyl peptidase 4 inhibitors as an alternative pharmacological intervention in subgroups of PCOS with high metabolic risk.

2. Main body

2.1. Gut-brain axis in controlling eating behavior

An inability to control eating behavior is the main culprit for eating beyond metabolic needs that result in obesity. Eating behavior is a complex pattern based on communication between specific regulatory and hedonistic centers in hypothalamus and peripheral signals from gastrointestinal tract. The latter system consists of gastric emptying/distention signals and gastrointestinal regulatory (orexigenic and anorexigenic) hormones. In addition, eating behavior is regulated also by cognitive functions and emotional inputs [8, 9].

Orexigenic hormone increases before meal and stimulates hunger and food intake. The most potent known orexigenic hormone ghrelin is released from specific endocrine cells in the stomach and stimulates food intake. On the opposite, hormones, such as cholecystokinin (CCK), peptide tyrosine-tyrosine (PYY) and glucagon-like polipeptide-1 (GLP-1), produce anorexigenic signals and affect peripheral organs and centers in the central nervous system (CNS) in order to stop feeding [8].

Reports about eating behavior in PCOS population are few and the results are not conclusive. It has not been established whether eating behavior is different in obese women with PCOS when compared to weight-matched non-PCOS controls. An increased food intake was reported in animal models and clinical studies with women with PCOS when compared to healthy controls [10–14]. Furthermore, bulimia was associated with an increased frequency

of PCOS, suggesting that androgens have appetite-stimulating effects and could impair the impulse control of eating behavior [15]. Disturbed appetite was also associated with altered opioid function demonstrated in PCOS linked to the stimulation of food intake and appetite for high fat/high glucose food through hedonistic centers in hypothalamus [16]. In addition, there are some evidences that disturbed regulation of gastrointestinal signals, in particular incretins, are intrinsic to PCOS [15, 17–21].

2.2. Incretin hormones

Incretins are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). They are polypeptide gut hormones secreted from endocrine cells in the small intestine under the influence of food intake and are responsible for 50–70% of postprandial insulin secretion. This is so-called incretin effect and is proportional to the current glycemia [8, 22].

GLP-1 is produced by L cells in distal intestine. It influences glucose hemostasis after food ingestion by insulin secretion and concurrent inhibition of glucagon release. GLP-1 is involved in the regulatory mechanisms of eating behavior with direct inhibitory effect on the homeostatic and hedonic centers of appetite in the central nervous system and indirect inhibitory effect on gastric emptying rates and gastrointestinal tract motility, which result in decreased food intake and consequently in body weight reduction [8, 23].

GIP is produced by K cells, which are located in the upper small intestine. It increases glucose-dependent insulin release and has protective effect on beta cell. GIP also increases lipogenesis and has bone protective and neuroprotective effect. In contrast to GLP1, no additional effects on appetite and body weight are shown with GIP [22].

Both incretin hormones have a short half-life. They are rapidly inactivated by the enzyme dipeptidyl peptidase 4 (DPP4).

Obesity with the onset of insulin resistance and consequent metabolic diseases, such as impaired glucose tolerance and type 2 diabetes, impairs the effect of incretins. Postprandial GLP-1 concentration in obese people is lower than in people with normal body weight [24–27]. Similarly, lower postprandial GLP-1 values were measured in patients with type 2 diabetes, while the GIP response in this population was preserved [28–32].

2.3. Incretin hormones in PCOS

Current reports about GLP-1 secretion in PCOS are not consistent. Some studies found similar fasting GLP-1 levels in PCOS compared with age- and BMI-matched controls [21, 33–35], whereas others reported decreased or increased fasting levels of GLP-1 in PCOS [36, 37]. Regarding postprandial levels of GLP-1, some authors demonstrated that postprandial plasma levels of GLP-1 did not differ between subjects with and without PCOS [20, 34, 35]. On the other hand, another study demonstrated lower GLP-1 levels in PCOS at the end of oral glucose tolerance test (OGTT) compared to the control group, whereas fasting GLP-1 levels did not differ between two groups [21]. However, lower fasting GLP-1 levels and a weakened GLP-1 response to standardized mixed meal in women with PCOS versus healthy control

group were also reported [37]. Contrary, another group found higher fasting GLP-1 levels in PCOS patients; while at the end of OGTT, GLP-1 levels did not differ between groups [36].

Also studies concerning the GLP-1 response in PCOS patients in relation to body weight are not conclusive. Some authors demonstrated no difference in GLP-1 between lean and obese patients with PCOS during OGTT, whereas others reported lower levels of GLP-1 in obese PCOS patients compared to lean age-matched PCOS patients and healthy lean controls [20].

There are only few studies evaluating GIP levels in women with PCOS. Compared with BMI- and age-matched controls, most of them demonstrated no difference in fasting GIP levels [20, 33–35, 38], yet some have found increased fasting GIP [21]. The results of postprandial GIP levels in PCOS compared to matched controls are more inconsistent. While some studies did not find differences in GIP levels [34], other found increased [21, 38] or decreased [20, 35] GIP levels after OGTT.

2.4. Therapeutic interventions targeting incretin system in obese PCOS

Weight reduction is substantial for improvement of hyperandrogenism and reproductive function in obese women with PCOS [4, 39]. Furthermore, weight loss has beneficial effects on all cardiovascular risk factors, including glycemic control, hypertension and hyperlipidemia in this population [39–41].

2.4.1. Lifestyle intervention in PCOS

Recent clinical practice guidelines recommend lifestyle modification as the first-line intervention in obese PCOS [42]. Low glucose index diet and hypocaloric diet lead to decrease in body mass index (BMI), waist circumference and waist-to-hip ratio [39]. Modification of lifestyle is associated with an important reduction in testosterone and an increase in serum sex hormone-binding globulin (SHBG) levels, leading to reduced free androgen index [43–45]. Furthermore, beneficial effect of appropriate lifestyle on metabolic abnormalities, such as a decrease in serum insulin and fasting glucose levels, an improvement in insulin resistance (IR) and decline in diastolic blood pressure, is known [43–45]. Lifestyle changes also lead to improvement of fertility function [39, 46, 47]. Two small studies in PCOS proved the impact of dietary intervention on ghrelin, whereas no studies evaluated the impact of lifestyle intervention on incretin hormones in this population [17, 48]. However, the treatment goals with lifestyle intervention are usually hardly achievable and nonsustainable in everyday life.

2.4.2. Metformin in PCOS

Metformin as an established treatment in PCOS with many potential roles, including attenuating IR and direct blocking ovarian androgen production, has inconsistently demonstrated weight reduction. The absolute weight loss that was best documented in obese rather in lean women with PCOS had been about 2.7 kg, representing less than 5% of weight reduction

[49, 50]. No benefit regarding weight reduction was recognized when metformin was added on lifestyle changes. In a small study with 19 lean and 21 obese PCOS patients, the impact of metformin on incretin hormones was demonstrated with the increase of GLP-1 during OGTT with 8-month metformin intervention [35].

2.4.3. GLP-1 receptor agonists in PCOS

The available recent data offer new opportunity to include an adjunct management in obese PCOS patients who have not responded to lifestyle modification with or without metformin [51, 52].

GLP-1 receptor agonists (GLP-1 RA) are class of antidiabetes medications, which are incretin mimetics. There are six GLP-1 RAs approved and available, of which only liraglutide and exenatide have been studied in PCOS [53–61]. Studies have been of short duration and have all shown the expected effective weight reduction with GLP-1Ras alone or in combination with metformin and improvement in glucose parameters with variable results on gynecological abnormalities and hyperandrogenism (**Table 1**).

2.4.3.1. Liraglutide in PCOS

Liraglutide is a long-acting GLP-1 RA analogue that is 97% homologous to human GLP-1. Its dose-dependent effect on weight loss was first observed in overweight patients with type 2 diabetes and later also in overweight subjects without diabetes. In dose of 3 mg, it was recently approved for weight management in many countries [62–65].

Study	Weight reduction	Improved eating behavior	Decreased insulin resistance	Decreased fasting and/or post-load glucose level	Reduced hyperandrogenism	Improved menstrual frequency
Elkind-Hirsch et al. [59]	x		x	x	x	x
Rasmussen and Lindenberg [55]	x					/
Kahal et al. [58]	x		/		/	
Jensterle Sever et al. [53]	x		/	x	/	/
Jensterle et al. [60]	x		x	x	/	x
Jensterle et al. [56]	x	x				
Jensterle et al. [57]	x		x	x	x	
Nylander et al. [61]	x				x	x

Note: x = yes; / = no effect.

Table 1. Reported effects of GLP-1 agonist treatment in women with PCOS.

The efficacy of 3 mg liraglutide on weight loss was studied in a Satiety and Clinical Adiposity-Liraglutide Evidence (SCALE) series of four trials involving 5358 patients who were divided in different patient categories. SCALE-prediabetes involved 3731 adult patients with prediabetes and BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² and associated hypertension or dyslipidemia [66]. SCALE-diabetes involved 846 adult patients with type 2 diabetes and BMI kg/m² ≥ 27 who were on per-oral hypoglycemic therapy [63]. In SCALE Maintenance trial, the ability of high-dose liraglutide to maintain weight lost following a low-calorie diet and exercise intervention was observed on 422 obese nondiabetic patients [67]. SCALE OSA involved 359 nondiabetic obese adults with moderate or severe obstructive sleep apnea, who were unable to use CPAP [68]. In composite data analysis of the SCALE clinical trials, liraglutide 3.0 mg led to 7.5% weight loss over 1 year.

Its impact on weight loss appears to be due to reduction of appetite, mediated partly through incretin effect and consequent suppress of ghrelin release and partly through its influence on gastric emptying via the autonomous nervous system [69]. Liraglutide is the only known glucose-lowering agent with proven ability to regulate eating behavior. It probably sufficiently activates mesolimbic GLP-1 receptor and suppresses hunger-driven feeding and reduces the hedonic value of food and food motivation [69]. It was demonstrated that liraglutide produces significant improvements in eating behavior in obese patients with T2DM and importantly reduces lust for fat intake. The effect was sustained 6 months after withdrawal of liraglutide [70, 71].

Current data about liraglutide use in obese patients with PCOS are very limited. In a 12-week study with 40 obese PCOS women who had been insufficiently treated with lifestyle modification and metformin regarding weight reduction, liraglutide 1.2 mg sc QD alone or in combination with metformin 1000 mg BID was associated with significantly greater weight loss when compared to metformin monotherapy. The mean weight loss in combined treatment was 6.5 kg. Liraglutide monotherapy resulted in 3.8 kg loss and metformin alone in 1.2 kg loss. The majority of patients who achieved at least 5% of weight reduction were on combination therapy. Two-hour post-load glucose level was significantly lower in the treatment groups with liraglutide. Menstrual frequency and androgen profile were not significantly changed in any group over the observed period [53]. Another study with newly diagnosed obese PCOS patients with high metabolic risk also showed significantly greater weight reduction with liraglutide therapy when compared to metformin and lifestyle intervention [54]. In both studies, liraglutide 1.2 mg QD was used before liraglutide in a dose of 3 mg was approved as an anti-obesity drug. In an observational study of 84 overweight and obese women with PCOS with mean duration of 27.8 weeks and with liraglutide doses ranging from 0.6 mg up to 1.8 mg per day, combined treatment with liraglutide and metformin was associated with significant weight reduction of 9 kg. More than 80% of patients lost at least 5% of baseline weight [55]. It was also reported that liraglutide treatment improved the impaired eating behavior of women with PCOS who were pre-treated with metformin and switched to liraglutide for 12 weeks. There was significant decrease in emotional eating that correlated with weight loss [56].

Adding metformin to liraglutide was proven as well-suited combination that enhances the therapeutic index of GLP-1RA and enables the use of lower liraglutide dose [57, 72–75]. Metformin in combination with low dose liraglutide 1.2 mg was superior to low dose

liraglutide 1.2 mg alone in reducing weight after 12 weeks in treatment naïve obese women with PCOS. Participants on combined treatment achieved clinically meaningful $\geq 5\%$ weight loss in almost 60% compared to about 40% of good responders with low dose liraglutide monotherapy. Androgens were lower in all patients at study completion, yet only androstenedione was significantly decreased in the combination group. Systolic blood pressure was significantly lowered in the liraglutide arm. All subjects demonstrated a significant improvement in insulin resistance and fasting and 2-hour post-load glucose level [57]. The observed benefits of GLP-1 RAs in combination with metformin are mechanistically well supported. In animal models and in humans with or without type 2 diabetes, administration of metformin led to increase in GLP-1 concentration [74, 75]. It directly stimulated GLP-1 production and secretion from L cells through crosstalk between the insulin and Wnt signaling pathways. In addition, its impact on alteration in bile acid absorption may result in increased GLP-1 secretion. Furthermore, it was demonstrated that metformin enhances expression of GLP1 receptors through a mechanism requiring PPAR-alpha [72]. It also has a small impact on the inhibition of DPP4 activity [76].

Another interesting avenue was opened with a study conducted with 57 women with PCOS received liraglutide for 12 weeks. Recognizing that the weight reducing effects of GLP-1 RAs are mediated through GLP-1 receptor, it was hypothesized that inter-individual difference in weight loss potential of liraglutide might be linked with genetic variability of GLP-1 receptor. It was demonstrated that a difference in a liraglutide-induced weight loss potential in phenotypically and metabolically homogeneous group of obese women with PCOS was based on some GLP1-R genotype [77].

The majority of available studies with liraglutide in PCOS did not focus on the cardiometabolic endpoints. In a small study, the potential impact of liraglutide on markers of liver fibrosis in PCOS was primarily investigated. Liraglutide was found to reduce procollagen type 3 amino terminal peptide, a predictor of liver cirrhosis. An average weight reduction of 3.0 kg achieved with larger dosage of 1.8 mg sc QD in monotherapy was observed over 24 weeks [78]. In another study, 6-month intervention with liraglutide was associated with significant reduction in atherothrombosis markers, including inflammation, endothelial function and clotting. The positive effect equally affected young obese women with PCOS and controls [58].

Few studies suggested an increase in menstrual frequencies when taking GLP-1 RAs [59–61]. The most recent study reported that liraglutide improved bleeding ratio and decreased ovarian volume with liraglutide when compared to placebo [61]. Moreover, after liraglutide discontinuation, one small 12-week study conducted with 40 infertile PCOS reported an increase of fertility potential. Women were randomized into three groups: MET group was treated with metformin 1000 mg BID, COMBI group was on combined treatment with metformin 1000 mg BID and liraglutide 1.2 mg QD and CON group were controls. CON directly proceeded with ovarian stimulation protocol, whereas MET and COMBI started with stimulation after 4-week washout period. More than 5% of weight reduction was achieved in over 75% in COMBI and about 45% of patients in metformin arm. In high responders who lost more than 5% of body weight, numbers of blastocysts/patient were greater in both treatment arms than in CON. High responders in COMBI had the highest number of oocytes/patient and of mature oocyte. In COMBI 3, patients became spontaneously pregnant before IVF in medication-free

period. The high rate of spontaneous pregnancies in COMBI after liraglutide discontinuation implies the potential role of GLP-1 in reproduction in the pre-conception period [79]. In line with these preliminary results, new data support a role for GLP-1RAs in fertility beyond merely weight reduction [51]. In animal models, GLP-1 and GLP receptors have been identified directly in the hypothalamo-pituitary ovary axis [80].

2.4.3.2. *Exenatide in PCOS*

The single report evaluating the effect of short-acting GLP-1 RA exenatide in PCOS was a 24-week randomized study demonstrated a mean weight loss of 3.2 kg with exenatide monotherapy in a dose of 10 µg twice daily, 6.0 kg with exenatide in adjunct to metformin and 1.6 kg with metformin alone. Combined therapy was superior to either monotherapy in improving menstrual frequency and ovulation rate. The ovulation rate was 86% in the combined group compared to 50% in exenatide monotherapy and 29% in metformin alone group. IR and insulin sensitivity were improved in all groups. Total cholesterol and triglyceride decreased with combined therapy compared to metformin alone [59]. Weight reductions with exenatide were of comparable magnitude to the liraglutide effect in PCOS, but achieved in a longer period of time with a larger drop out [53, 59]. The study with exenatide was the first study addressing intervention with GLP-1 Ras in PCOS population.

2.4.3.3. *Safety profile of GLP-RAs in PCOS*

GLP1Ras appear to be well tolerated in PCOS population. The main side effect was nausea, which was transient and did not result in study withdrawals. In studies when GLP-1RA liraglutide was dosed at 1.2 mg (the middle dose for diabetes therapy) and combined with metformin in maximum dose (1 g BID), nausea appeared to be less common, which may be due to the lower doses of liraglutide administered [57, 60]. So far, there is no safety data about GLP-1RA use in pregnancy. They are generally classified as pregnancy class C. Therefore, the use of these medications in this population would require use of contraception while on therapy. Counseling women who are planning pregnancy would include a washout period.

2.4.4. *PDE4 inhibitors in PCOS*

Less recognized and completely distinct regulatory mechanisms related to the enhancement of GLP-1-mediated action represent an inhibition of phosphodiesterase (PDE) 4. The first drug specifically targeting PDE4 was roflumilast. It was approved for treatment of chronic inflammatory diseases, primarily chronic obstructive pulmonary disease (COPD), due to its efficient anti-inflammatory effect [81]. Collaterally, 1-year treatment of COPD with roflumilast was associated with a weight loss of about 2 kg within 12 months [81]. Beneficial effect of roflumilast on metabolic parameters and glucose homeostasis accompanied with mean weight reduction of approximately 2 kg versus placebo was also demonstrated with a short-term use of roflumilast in newly diagnosed T2DM without COPD [82]. A small randomized study with obese PCOS women demonstrated that treatment with roflumilast 500 mg per day in combination with metformin 1000 mg twice per day significantly reduced body weight in obese PCOS when compared to metformin monotherapy. Weight loss was primarily due to visceral fat mass reduction with the between treatment difference of about 5 kg [83]. These observations gave rise to the hypothesis that PDE4

is involved in regulation of signaling pathways linked to GLP-1 release [84]. In line with this consideration are data from experimental rodent model where a single treatment with roflumilast enhanced plasma GLP-1 levels up to 2.5-fold [84]. A direct comparison of short-term intervention with liraglutide and roflumilast addressing weight management was performed in PCOS-related obesity [60]. It was demonstrated that both monotherapy with liraglutide and roflumilast were associated with significant weight reduction in obese PCOS when compared to metformin monotherapy. Reduction of weight with liraglutide was greater than with roflumilast [60].

2.4.5. DPP4 inhibitors in PCOS

The endogenous incretins are quickly degraded by DPP4 in serum. Degradation of endogenous incretins can be prevented by DPP4 inhibitors. DPP4 inhibitors are taken orally and are used as antidiabetic agents. They influence glucose homeostasis through the enhancement of endogenous incretion hormones. As incretin enhances insulin secretion in response to meal, DPP4 inhibitors do not cause hypoglycemia. They have been reported to cause a 0.5–1% HbA1c reduction [85, 86]. Five DPP4 inhibitors are approved in the treatment of type 2 diabetes: sitagliptin, alogliptin, saxagliptin, vildagliptin and linagliptin. The role of enhancement of endogenous GLP-1 with DPP4 inhibitors in the treatment of obese PCOS patient is yet to be established. So far, only sitagliptin, alogliptin and saxagliptin were studied in PCOS (**Table 2**).

The present evidences suggest that DPP4 inhibitors preserve beta cell function [23, 87]. The fact that body weight gain and associated insulin resistance lead to increased load of beta cells and consequent beta cell dysfunction give rise to thoughts that the use of DPP4 inhibitors in treatment of PCOS with high metabolic risk is reasonable.

Another aspect is weight management. The enhancement of endogenous incretin hormones by DPP4 inhibitors is generally described as being weight neutral, although modest weight reduction has been seen in some clinical trials, particularly when DPP4 inhibitors are used

Study	DPP4 inhibitor	Beta cell function	Insulin sensitivity	Insulin resistance	T2DM development	Weight
Jensterle et al. [92]	Alogliptin	Improved	Increased	Decreased		
Ferjan et al. [93]	Sitagliptin	Improved			Decreased	Less weight gain compared to lifestyle
Elkind-Hirsch et al. [94]	Saxagliptin	Improved	Increased	Decreased	Decreased	Reduction
Jensterle Sever et al. [95]	Sitagliptin					In combination with metformin less weight gain compared to metformin monotherapy

Table 2. Reported effects of treatment with DPP4 inhibitors in women with PCOS.

in combination with metformin [88, 89]. Nevertheless, the mere fact that DPP4 inhibition is not associated with the weight gain that typically accompanies improved glycemic control in patients with T2DM suggests that DPP4 inhibitors may not be completely neutral in this respect [90]. Slowing of gastric emptying that might reinforce the sustained change of eating behavior was also demonstrated with treatment with DPP4 inhibitor sitagliptin [91].

The first study addressing the preservation of beta cell function in PCOS with DPP4 inhibitor reported an increase of insulin sensitivity and significant decrease of insulin resistance when alogliptin was added to metformin. Even greater improvement of these parameters was seen when triplet therapy with alogliptin, pioglitazone and metformin was used [92]. Beneficial effects of another DPP4 inhibitor sitagliptin were recently reported in metformin intolerant women with PCOS and high metabolic risk. After metformin withdrawal, a 12-week treatment with sitagliptin leads to significant improvement in beta cell function and prevented conversion rate from normal to impaired glucose tolerance and type 2 diabetes when compared to placebo [93]. Preliminary data suggest that DPP4 inhibitors seem to be a promising alternative in PCOS women with high metabolic risk who have failed with lifestyle intervention and are metformin intolerant. Future larger designs of longer duration should be powered.

A small single blind, randomized study on prediabetic PCOS women reported beneficial effect of DPP4 inhibitor saxagliptin on glucose homeostasis, metabolic parameters and clinical status. A 16-week intervention with saxagliptin/metformin (5 mg/2000 mg), monotherapy with saxagliptin (5 mg) and monotherapy with metformin (2000 mg) lead to normalization in glucose homeostasis in 91, 55 and 25% of patients, respectively. Improvement of metabolic parameters and clinical status was reported in all groups [94].

In a recent randomized study, another potential use of DPP4 inhibitors was demonstrated. Enhancement of endogenous GLP-1 signaling by sitagliptin prevented the expected weight regain after liraglutide 3.0 mg cessation in women with PCOS. During a 12-week follow-up period, sitagliptin in adjunct to metformin resulted in weight maintenance, whereas a switch to metformin alone resulted in a significant weight regain after liraglutide discontinuation. It was also demonstrated that the ability to resist emotional eating was greater in combined treatment than in monotherapy with metformin [95]. The observation provides first clinical findings suggesting that DPP4 inhibition may prevent weight regain after liraglutide cessation. This sequential treatment concept is particularly useful in patients who became intolerant, develop treatment resistance or decide to stop the antiobesity treatment with liraglutide. Further research is necessary to fully understand the cross talks between effects of peripheral signals of endogenous GLP-1 and central areas of satiety and reward in obese subjects.

2.4.6. *Bariatric surgery in PCOS*

Bariatric surgery is a well-established and effective method for the treatment of extreme obesity for well-informed and motivated patients with a BMI > 40 kg/m² or >35 kg/m², with at least one comorbidity related to obesity and who have been previously unsuccessful with medical treatment for obesity [96]. The mechanism of weight loss induced by bariatric surgery is multifactorial. Beside reduced gastric volume [97, 98], weight reduction could be possibly explained with the changes in gut-brain axis. Gastrointestinal bypass surgery results in a quick delivery of nutrients to the small intestine associated with large increase in postprandial levels of GLP1 and PYY hormones

[97–100]. Nevertheless, the mere fact that postoperative weight loss was significantly correlated to the magnitude of GLP1 response (57 Holst) suggests that GLP1 has major role in weight balance.

There is currently no clear consensus on the role of bariatric surgery in the treatment of obese patients with PCOS. Studies in PCOS are very heterogeneous with a small number of patients. Beneficial observations were reported after laparoscopic Roux-en-Y gastric band (RYGB) operation, in two small studies, where post-operational weight loss was associated with resolution of hirsutism in 29–52% of patients, resolution of type 2 diabetes, improvement of hypertension and dyslipidemia was also reported. Moreover, in both studies, significant improvement in conception rate was observed [101, 102]. The same effects were also reported in small studies on obese PCOS patients who underwent gastric banding, gastric plication and laparoscopic sleeve gastrectomy [103, 104].

3. Conclusion

Agents mediating through GLP-1 effects in combination with lifestyle intervention and metformin could potentially improve treatment outcomes in obese PCOS via co-targeting multifactorial origin of obesity and concomitant abnormalities intrinsically related to PCOS. Based on the limited available data, GLP-1RAs, in particular liraglutide, should be considered in obese PCOS. Enhanced understanding of the direct impact on GLP-1 beyond weight reducing and metabolic effects at the levels of pituitary and ovary are expected within the next 5 years [51]. Larger and longer randomized studies are needed to establish metabolic, reproductive and cardiovascular risk reduction and assess sustainability and safety profile of the benefits achieved by these potential new treatment strategies.

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