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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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References

- [1] Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: A systematic review and meta-analysis. *Human Reproduction Update*. 2012;**18**(6):618-637. DOI: 10.1093/humupd/dms030
- [2] De Leo V, la Marca A, Petraglia F. Insulin-lowering agents in the management of polycystic ovary syndrome. *Endocrine Reviews*. 2003;**24**(5):633-667. DOI: 10.1210/er.2002-0015

- [3] Lass N, Kleber M, Winkel K, Wunsch R, Reinehr T. Effect of lifestyle intervention on features of polycystic ovarian syndrome, metabolic syndrome, and intima-media thickness in obese adolescent girls. *The Journal of Clinical Endocrinology and Metabolism*. 2011;**96**(11):3533-3540. DOI: 10.1210/jc.2011-1609
- [4] Crosignani PG, Colombo M, Vegetti W, Somigliana E, Gessati A, Ragni G. Overweight and obese anovulatory patients with polycystic ovaries: Parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet. *Human Reproduction* (Oxford, England). 2003;**18**(9):1928-1932. DOI: 10.1093/humrep/deg367
- [5] Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: A systematic review and meta-analysis. *Human Reproduction Update*. 2010;**16**(4):347-363. DOI: 10.1093/humupd/dmq001
- [6] Elting MW, Korsen TJ, Bezemer PD, Schoemaker J. Prevalence of diabetes mellitus, hypertension and cardiac complaints in a follow-up study of a Dutch PCOS population. *Human Reproduction* (Oxford, England). 2001;**16**(3):556-560. DOI: 10.1093/humrep/16.3.556
- [7] Legro RS, Kusanman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: A prospective, controlled study in 254 affected women. *The Journal of Clinical Endocrinology and Metabolism*. 1999;**84**(1):165-169. DOI: 10.1210/jc.84.1.165
- [8] Woods SC, D'Alessio DA. Central control of body weight and appetite. *The Journal of Clinical Endocrinology and Metabolism*. 2008;**93**(11 Suppl 1):S37-S50. DOI: 10.1210/jc.2008-1630
- [9] Saydam BO, Yildiz BO. Gut-brain axis and metabolism in polycystic ovary syndrome. *Current Pharmaceutical Design*. 2016;**22**:1-16. DOI: 10.2174/1381612822666160715
- [10] Douglas CC, Norris LE, Oster RA, Darnell BE, Azziz R, Gower BA. Difference in dietary intake between women with polycystic ovary syndrome and healthy controls. *Fertility and Sterility*. 2006;**86**(2):411-417. DOI: 10.1016/j.fertnstert.2005.12.054
- [11] Zhang J, Liu Y, Liu X, Xu L, Zhou L, Tang L, et al. High intake of energy and fat in Southwest Chinese women with PCOS: A population-based case-control study. *PLoS One*. 2015;**10**(5):e0127094. DOI: 10.1371/journal.pone.0127094
- [12] Ahmadi A, Akbarzadeh M, Mohammadi F, Akbari M, Jafari B, Tolide-Ie HR. Anthropometric characteristics and dietary pattern of women with polycystic ovary syndrome. *Indian Journal of Endocrinology and Metabolism*. 2013;**17**(4):672-676. DOI: 10.4103/2230-8210.113759
- [13] Graff SK, Mário FM, Alves BC, Spritzer PM. Dietary glycemic index is associated with less favorable anthropometric and metabolic profiles in polycystic ovary syndrome women with different phenotypes. *Fertility and Sterility*. 2013;**100**(4):1081-1088. DOI: 10.1016/j.fertnstert.2013.06.005

- [14] Moran LJ, Ranasinha S, Zoungas S, McNaughton SA, Brown WJ, Teede HJ. The contribution of diet, physical activity and sedentary behaviour to body mass index in women with and without polycystic ovary syndrome. *Human Reproduction (Oxford, England)*. 2013;**28**(8):2276-2283. DOI: 10.1093/humrep/det256
- [15] Naessén S, Carlström K, Garoff L, Glant R, Hirschberg AL. Polycystic ovary syndrome in bulimic women—An evaluation based on the new diagnostic criteria. *Gynecological Endocrinology: The Official Journal of the International Society of Gynecological Endocrinology*. 2006;**22**(7):388-394. DOI: 10.1080/09513590600847421
- [16] Berent-Spillon A, Love T, Pop-Busui R, Sowers M, Persad CC, Pennington KP, et al. Insulin resistance influences central opioid activity in polycystic ovary syndrome. *Fertility and Sterility*. 2011;**95**(8):2494-2498. DOI: 10.1016/j.fertnstert.2011.03.031
- [17] Moran LJ, Noakes M, Clifton PM, Wittert GA, Tomlinson L, Galletly C, et al. Ghrelin and measures of satiety are altered in polycystic ovary syndrome but not differentially affected by diet composition. *The Journal of Clinical Endocrinology and Metabolism*. 2004;**89**(7):3337-3344. DOI: 10.1210/jc.2003-031583
- [18] Moran LJ, Noakes M, Clifton PM, Wittert GA, Roux CWL, Ghatei MA, et al. Postprandial ghrelin, cholecystokinin, peptide YY, and appetite before and after weight loss in overweight women with and without polycystic ovary syndrome. *The American Journal of Clinical Nutrition*. 2007;**86**(6):1603-1610
- [19] Daghestani MH, Daghestani MH, El-Mazny A. Circulating ghrelin levels and the polycystic ovary syndrome: Correlation with the clinical, hormonal and metabolic features. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*. 2011;**155**(1):65-68. DOI: 10.1016/j.ejogrb.2010.11.019
- [20] Pontikis C, Yavropoulou MP, Toulis KA, Kotsa K, Kazakos K, Papazisi A, et al. The incretin effect and secretion in obese and lean women with polycystic ovary syndrome: A pilot study. *Journal of Women's Health (2002)*. 2011;**20**(6):971-976. DOI: 10.1089/jwh.2010.2272
- [21] Vrbikova J, Hill M, Bendlova B, Grimmichova T, Dvorakova K, Vondra K, et al. Incretin levels in polycystic ovary syndrome. *European Journal of Endocrinology*. 2008;**159**(2):121-127. DOI: 10.1530/EJE-08-0097
- [22] Phillips LK, Prins JB. Update on incretin hormones. *Annals of the New York Academy of Sciences*. 2011;**1243**:E55-E74. DOI: 10.1111/j.1749-6632.2012.06491.x
- [23] Garber AJ. Incretin therapy – Present and future. *The Review of Diabetic Studies: RDS*. 2011;**8**(3):307-322. DOI: 10.1900/RDS.2011.8.307
- [24] Hussein MS, Abushady MM, Refaat S, Ibrahim R. Plasma level of glucagon-like peptide 1 in obese Egyptians with normal and impaired glucose tolerance. *Archives of Medical Research*. 2014;**45**(1):58-62. DOI: 10.1016/j.arcmed.2013.10.012

- [25] de Luis DA, Aller R, Conde R, Primo D, Izaola O, Castro MJ, et al. Basal glucagon-like peptide 1 levels and metabolic syndrome in obese patients. *Journal of Investigative Medicine: The Official Publication of the American Federation for Clinical Research*. 2012;**60**(6):874-877. DOI: 10.2310/JIM.0b013e3182544f9e
- [26] Carr RD, Larsen MO, Jelic K, Lindgren O, Vikman J, Holst JJ, et al. Secretion and dipeptidyl peptidase-4-mediated metabolism of incretin hormones after a mixed meal or glucose ingestion in obese compared to lean, nondiabetic men. *The Journal of Clinical Endocrinology and Metabolism*. 2010;**95**(2):872-878. DOI: 10.1210/jc.2009-2054
- [27] Muscelli E, Mari A, Casolaro A, Camastra S, Seghieri G, Gastaldelli A, et al. Separate impact of obesity and glucose tolerance on the incretin effect in normal subjects and type 2 diabetic patients. *Diabetes*. 2008;**57**(5):1340-1348. DOI: 10.2337/db07-1315
- [28] Nauck M, Stöckmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in Type 2 (non-insulin-dependent) diabetes. *Diabetologia*. 1986;**29**(1):46-52. DOI: 10.1007/BF02427280
- [29] Vilsbøll T, Holst JJ. Incretins, insulin secretion and Type 2 diabetes mellitus. *Diabetologia*. 2004;**47**(3):357-366. DOI: 10.1007/s00125-004-1342-6
- [30] Vaag AA, Holst JJ, Vølund A, Beck-Nielsen H. Gut incretin hormones in identical twins discordant for non-insulin-dependent diabetes mellitus (NIDDM)—Evidence for decreased glucagon-like peptide 1 secretion during oral glucose ingestion in NIDDM twins. *European Journal of Endocrinology*. 1996;**135**(4):425-432
- [31] Toft-Nielsen M-B, Damholt MB, Madsbad S, Hilsted LM, Hughes TE, Michelsen BK, et al. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *The Journal of Clinical Endocrinology and Metabolism*. 2001;**86**(8):3717-3723. DOI: 10.1210/jc.86.8.3717
- [32] Holst JJ, Gromada J. Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans. *American Journal of Physiology. Endocrinology and Metabolism*. 2004;**287**(2):E199-E206. DOI: 10.1152/ajpendo.00545.2003
- [33] Cassar S, Teede HJ, Harrison CL, Joham AE, Moran LJ, Stepto NK. Biomarkers and insulin sensitivity in women with Polycystic Ovary Syndrome: Characteristics and predictive capacity. *Clinical Endocrinology (Oxford)*. 2015;**83**(1):50-58. DOI: 10.1111/cen.12619
- [34] Gama R, Norris F, Wright J, Morgan L, Hampton S, Watkins K, et al. The entero-insular axis in polycystic ovarian syndrome. *Annals of Clinical Biochemistry*. 1996;**33**(3):190-195
- [35] Svendsen PF, Nilas L, Madsbad S, Holst JJ. Incretin hormone secretion in women with polycystic ovary syndrome: Roles of obesity, insulin sensitivity, and treatment with metformin. *Metabolism*. 2009;**58**(5):586-593. DOI: 10.1016/j.metabol.2008.11.009
- [36] Lin T, Li S, Xu H, Zhou H, Feng R, Liu W, et al. Gastrointestinal hormone secretion in women with polycystic ovary syndrome: An observational study. *Human Reproduction (Oxford, England)*. 2015;**30**(11):2639-2644. DOI: 10.1093/humrep/dev231

- [37] Aydin K, Arusoglu G, Koksall G, Cinar N, Yazgan Aksoy D, Yildiz BO. Fasting and post-prandial glucagon like peptide 1 and oral contraception in polycystic ovary syndrome. *Clinical Endocrinology (Oxford)*. 2014;**81**(4):588-592. DOI: 10.1111/cen.12468
- [38] Chang CL, Huang SY, Soong YK, Cheng PJ, Wang C-J, Liang IT. Circulating irisin and glucose-dependent insulintropic peptide are associated with the development of polycystic ovary syndrome. *The Journal of Clinical Endocrinology and Metabolism*. 2014;**99**(12):E2539-E2548. DOI: 10.1210/jc.2014-1180
- [39] Thomson RL, Buckley JD, Noakes M, Clifton PM, Norman RJ, Brinkworth GD. The effect of a hypocaloric diet with and without exercise training on body composition, cardio-metabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome. *The Journal of Clinical Endocrinology and Metabolism*. 2008;**93**(9):3373-3380. DOI: 10.1210/jc.2008-0751
- [40] Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database of Systematic Reviews*. 2011;(7):CD007506. DOI: 10.1002/14651858.CD007506.pub3
- [41] Haqq L, McFarlane J, Dieberg G, Smart N. Effect of lifestyle intervention on the reproductive endocrine profile in women with polycystic ovarian syndrome: A systematic review and meta-analysis. *Endocrine Connections*. 2014;**3**(1):36-46. DOI: 10.1530/EC-14-0010
- [42] National Institute for Health and Clinical Excellence Obesity. Guidance on the Prevention, Identification, Assessment and Management of Overweight and Obesity in Adults and Children. NICE Clin Guidel 2006 [Internet] Available from: <https://www.nice.org.uk/guidance/cg43> [Accessed: July 30, 2017]
- [43] Clark AM, Ledger W, Galletly C, Tomlinson L, Blaney F, Wang X, et al. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. *Human Reproduction (Oxford, England)*. 1995;**10**(10):2705-2712
- [44] Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. *Human Reproduction (Oxford, England)*. 1998;**13**(6):1502-1505. DOI: 10.1093/humrep/13.6.1502
- [45] Huber-Buchholz MM, Carey DG, Norman RJ. Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: Role of insulin sensitivity and luteinizing hormone. *The Journal of Clinical Endocrinology and Metabolism*. 1999;**84**(4):1470-1474. DOI: 10.1210/jcem.84.4.5596
- [46] Marsh KA, Steinbeck KS, Atkinson FS, Petocz P, Brand-Miller JC. Effect of a low glycemic index compared with a conventional healthy diet on polycystic ovary syndrome. *The American Journal of Clinical Nutrition*. 2010;**92**(1):83-92. DOI: 10.3945/ajcn.2010.29261
- [47] Kiddy DS, Hamilton-Fairley D, Bush A, Short F, Anyaoku V, Reed MJ, et al. Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. *Clinical Endocrinology (Oxford)*. 1992;**36**(1):105-111. DOI: 10.1111/j.1365-2265.1992.tb02909.x

- [48] Gambineri A, Pagotto U, Tschöp M, Vicennati V, Manicardi E, Carcello A, et al. Anti-androgen treatment increases circulating ghrelin levels in obese women with polycystic ovary syndrome. *Journal of Endocrinological Investigation*. 2003;**26**(7):629-634
- [49] Nieuwenhuis-Ruifrok AE, Kuchenbecker WKH, Hoek A, Middleton P, Norman RJ. Insulin sensitizing drugs for weight loss in women of reproductive age who are overweight or obese: Systematic review and meta-analysis. *Human Reproduction Update*. 2009;**15**(1):57-68. DOI: 10.1093/humupd/dmn043
- [50] Padwal R, Li SK, Lau DCW. Long-term pharmacotherapy for overweight and obesity: A systematic review and meta-analysis of randomized controlled trials. *International Journal of Obesity and Related Metabolic Disorders: Journal of the International Association for the Study of Obesity*. 2003;**27**(12):1437-1446. DOI: 10.1038/sj.ijo.0802475
- [51] Lamos EM, Malek R, Davis SN. GLP-1 receptor agonists in the treatment of polycystic ovary syndrome. *Expert Review of Clinical Pharmacology*. 2017;**10**(4):401-408. DOI: 10.1080/17512433.2017.1292125
- [52] Niafar M, Pourafkari L, Porhomayon J, Nader N. A systematic review of GLP-1 agonists on the metabolic syndrome in women with polycystic ovaries. *Archives of Gynecology and Obstetrics*. 2016;**293**(3):509-515. DOI: 10.1007/s00404-015-3976-7
- [53] Jensterle Sever M, Kocjan T, Pfeifer M, Kravos NA, Janez A. Short-term combined treatment with liraglutide and metformin leads to significant weight loss in obese women with polycystic ovary syndrome and previous poor response to metformin. *European Journal of Endocrinology*. 2014;**170**(3):451-459. DOI: 10.1530/EJE-13-0797
- [54] Jensterle M, Kravos NA, Pfeifer M, Kocjan T, Janez A. A 12-week treatment with the long-acting glucagon-like peptide 1 receptor agonist liraglutide leads to significant weight loss in a subset of obese women with newly diagnosed polycystic ovary syndrome. *Hormones (Athens, Greece)*. 2015;**14**(1):81-90
- [55] Rasmussen CB, Lindenberg S. The effect of liraglutide on weight loss in women with polycystic ovary syndrome: An observational study. *Frontiers in Endocrinology*. 2014;**5**:140. DOI: 10.3389/fendo.2014.00140
- [56] Jensterle M, Kocjan T, Kravos NA, Pfeifer M, Janez A. Short-term intervention with liraglutide improved eating behavior in obese women with polycystic ovary syndrome. *Endocrine Research*. 2015;**40**(3):133-138. DOI: 10.3109/07435800.2014.966385
- [57] Jensterle M, Goricar K, Janez A. Metformin as an initial adjunct to low-dose liraglutide enhances the weight-decreasing potential of liraglutide in obese polycystic ovary syndrome: Randomized control study. *Experimental and Therapeutic Medicine*. 2016;**11**:1194-1200. DOI: 10.3892/etm.2016.3081
- [58] Kahal H, Aburima A, Ungvari T, Rigby AS, Coady AM, Vince RV, et al. The effects of treatment with liraglutide on atherothrombotic risk in obese young women with polycystic ovary syndrome and controls. *BMC Endocrine Disorders*. 2015;**15**:14. DOI: 10.1186/s12902-015-0005-6

- [59] Elkind-Hirsch K, Marrioneaux O, Bhushan M, Vernor D, Bhushan R. Comparison of single and combined treatment with exenatide and metformin on menstrual cyclicity in overweight women with polycystic ovary syndrome. *The Journal of Clinical Endocrinology and Metabolism*. 2008;**93**(7):2670-2678. DOI: 10.1210/jc.2008-0115
- [60] Jensterle M, Salamun V, Kocjan T, Vrtacnik Bokal E, Janez A. Short term monotherapy with GLP-1 receptor agonist liraglutide or PDE 4 inhibitor roflumilast is superior to metformin in weight loss in obese PCOS women: A pilot randomized study. *Journal of Ovarian Research*. 2015;**8**:32. DOI: 10.1186/s13048-015-0161-3
- [61] Nylander M, Frøssing S, Clausen HV, Kistorp C, Faber J, Skouby SO. Effects of liraglutide on ovarian dysfunction in polycystic ovary syndrome: A randomized clinical trial. *Reproductive Biomedicine Online*. 2017;**35**(1):121-127. DOI: 10.1016/j.rbmo.2017.03.023
- [62] Astrup A, Rössner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, et al. Effects of liraglutide in the treatment of obesity: A randomised, double-blind, placebo-controlled study. *Lancet (London, England)*. 2009;**374**(9701):1606-1616. DOI: 10.1016/S0140-6736(09)61375-1
- [63] Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjøth TV, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: The SCALE diabetes randomized clinical trial. *Journal of the American Medical Association*. 2015;**314**(7):687-699. DOI: 10.1001/jama.2015.9676
- [64] Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: Systematic review and meta-analyses of randomised controlled trials. *British Medical Journal*. 2012;**344**:d7771. DOI: 10.1136/bmj.d7771
- [65] Wilding JPH, Overgaard RV, Jacobsen LV, Jensen CB, le Roux CW. Exposure-response analyses of liraglutide 3.0 mg for weight management. *Diabetes, Obesity & Metabolism*. 2016;**18**(5):491-499. DOI: 10.1111/dom.12639
- [66] Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *The New England Journal of Medicine*. 2015;**373**(1):11-22. DOI: 10.1056/NEJMoa1411892
- [67] Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: The SCALE Maintenance randomized study. *International Journal of Obesity (2005)*. 2013;**37**(11):1443-1451. DOI: 10.1038/ijo.2013.120
- [68] Collier A, Blackman A, Foster G, Zammit G, Rosenberg R, Wadden T, et al. S28 liraglutide 3.0 mg reduces severity of obstructive sleep apnoea and body weight in obese individuals with moderate or severe disease: Scale sleep apnoea trial. *Thorax*. 2014;**69**(Suppl 2):A16-A17. DOI: 10.1136/thoraxjnl-2014-206260.34
- [69] Skibicka KP. The central GLP-1: Implications for food and drug reward. *Frontiers in Neuroscience*. 2013;**7**:181. DOI: 10.3389/fnins.2013.00181

- [70] Keskitalo K, Tuorila H, Spector TD, Cherkas LF, Knaapila A, Kaprio J, et al. The Three-Factor Eating Questionnaire, body mass index, and responses to sweet and salty fatty foods: A twin study of genetic and environmental associations. *The American Journal of Clinical Nutrition*. 2008;**88**(2):263-271
- [71] Inoue K, Maeda N, Kashine S, Fujishima Y, Kozawa J, Hiuge-Shimizu A, et al. Short-term effects of liraglutide on visceral fat adiposity, appetite, and food preference: A pilot study of obese Japanese patients with type 2 diabetes. *Cardiovascular Diabetology*. 2011;**10**:109. DOI: 10.1186/1475-2840-10-109
- [72] Maida A, Lamont BJ, Cao X, Drucker DJ. Metformin regulates the incretin receptor axis via a pathway dependent on peroxisome proliferator-activated receptor- α in mice. *Diabetologia*. 2011;**54**(2):339-349. DOI: 10.1007/s00125-010-1937-z
- [73] Mannucci E, Ognibene A, Cremasco F, Bardini G, Mencucci A, Pierazzuoli E, et al. Effect of metformin on glucagon-like peptide 1 (GLP-1) and leptin levels in obese nondiabetic subjects. *Diabetes Care*. 2001;**24**(3):489-494. DOI: 10.2337/diacare.24.3.489
- [74] Mannucci E, Tesi F, Bardini G, Ognibene A, Petracca MG, Ciani S, et al. Effects of metformin on glucagon-like peptide-1 levels in obese patients with and without Type 2 diabetes. *Diabetes, Nutrition & Metabolism*. 2004;**17**(6):336-342
- [75] Yasuda N, Inoue T, Nagakura T, Yamazaki K, Kira K, Saeki T, et al. Enhanced secretion of glucagon-like peptide 1 by biguanide compounds. *Biochemical and Biophysical Research Communications*. 2002;**298**(5):779-784. DOI: 10.1016/S0006-291X(02)02565-2
- [76] D'Alessio DA. What if gut hormones aren't really hormones: DPP-4 inhibition and local action of GLP-1 in the gastrointestinal tract. *Endocrinology*. 2011;**152**(8):2925-2926. DOI: 10.1210/en.2011-1385
- [77] Jensterle M, Pirš B, Goričar K, Dolžan V, Janež A. Genetic variability in GLP-1 receptor is associated with inter-individual differences in weight lowering potential of liraglutide in obese women with PCOS: A pilot study. *European Journal of Clinical Pharmacology*. 2015;**71**:817-824. DOI: 10.1007/s00228-015-1868-1
- [78] Kahal H, Abouda G, Rigby AS, Coady AM, Kilpatrick ES, Atkin SL. Glucagon-like peptide-1 analogue, liraglutide, improves liver fibrosis markers in obese women with polycystic ovary syndrome and nonalcoholic fatty liver disease. *Clinical Endocrinology (Oxford)*. 2014;**81**(4):523-528. DOI: 10.1111/cen.12369
- [79] Jensterle-Sever M, Šalamun V, Vrtačnik-Bokal E, Janež A. Short-term intervention with liraglutide and metformin increased fertility potential in a subset of obese women with PCOS proceeding in vitro fertilization. *Endocrine Reviews*. 2017;**38**(3 Suppl):SAT 095 DOI: 10.1186/s12902-017-0155-9. ISSN: 1945-7189
- [80] Shimizu I, Hirota M, Ohboshi C, Shima K. Identification and localization of glucagon-like peptide-1 and its receptor in rat brain. *Endocrinology*. 1987;**121**(3):1076-1082. DOI: 10.1210/endo-121-3-1076

- [81] Fabbri LM, Calverley PMA, Izquierdo-Alonso JL, Bundschuh DS, Brose M, Martinez FJ, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with long-acting bronchodilators: Two randomised clinical trials. *Lancet* (London, England). 2009;**374**(9691):695-703. DOI: 10.1016/S0140-6736(09)61252-6
- [82] Wouters EFM, Bredenbröker D, Teichmann P, Brose M, Rabe KF, Fabbri LM, et al. Effect of the phosphodiesterase 4 inhibitor roflumilast on glucose metabolism in patients with treatment-naïve, newly diagnosed type 2 diabetes mellitus. *The Journal of Clinical Endocrinology and Metabolism*. 2012;**97**(9):E1720-E1725. DOI: [doi.org/10.1210/jc.2011-2886](http://dx.doi.org/10.1210/jc.2011-2886)
- [83] Jensterle M, Kocjan T, Janez A. Phosphodiesterase 4 inhibition as a potential new therapeutic target in obese women with polycystic ovary syndrome. *The Journal of Clinical Endocrinology and Metabolism*. 2014;**99**(8):E1476-E1481. DOI: 10.1210/jc.2014-1430
- [84] Vollert S, Kaessner N, Heuser A, Hanauer G, Dieckmann A, Knaack D, et al. The glucose-lowering effects of the PDE4 inhibitors roflumilast and roflumilast-N-oxide in db/db mice. *Diabetologia*. 2012;**55**(10):2779-2788. DOI: 10.1007/s00125-012-2632-z
- [85] Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: Systematic review and meta-analysis. *Journal of the American Medical Association*. 2007;**298**(2):194-206. DOI: 10.1001/jama.298.2.194
- [86] Khoo J, Rayner CK, Jones KL, Horowitz M. Incretin-based therapies: New treatments for type 2 diabetes in the new millennium. *Therapeutics and Clinical Risk Management*. 2009;**5**(3):683-698. DOI: 10.2147/TCRM.S4975
- [87] Holst JJ, Deacon CF. Is there a place for incretin therapies in obesity and prediabetes? *Trends in Endocrinology and Metabolism: TEM*. 2013;**24**(3):145-152. DOI: 10.1016/j.tem.2013.01.004
- [88] Phung OJ, Scholle JM, Talwar M, Coleman CI. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. *Journal of the American Medical Association*. 2010;**303**(14):1410-1418. DOI: 10.1001/jama.2010.405
- [89] Aroda VR, Henry RR, Han J, Huang W, DeYoung MB, Darsow T, et al. Efficacy of GLP-1 receptor agonists and DPP-4 inhibitors: Meta-analysis and systematic review. *Clinical Therapeutics*. 2012;**34**(6):1247-1258.e22. DOI: 10.1016/j.clinthera.2012.04.013
- [90] Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* (London, England). 1998;**352**(9131):837-853. DOI: 10.1016/S0140-6736(98)07019-6
- [91] Aulinger BA, Bedorf A, Kutscherauer G, de Heer J, Holst JJ, Göke B, et al. Defining the role of GLP-1 in the enteroinsular axis in type 2 diabetes using DPP-4 inhibition and GLP-1 receptor blockade. *Diabetes*. 2014;**63**(3):1079-1092. DOI: 10.2337/db13-1455

- [92] Jensterle M, Goricar K, Janez A. Add on DPP-4 inhibitor alogliptin alone or in combination with pioglitazone improved β -cell function and insulin sensitivity in metformin treated PCOS. *Endocrine Research*. 2017;1-8. DOI: 10.1080/07435800.2017.1294602
- [93] Ferjan S, Janež A, Jensterle M. Dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin improved beta cell function and prevented a conversion rate to IGT and DM2 in metformin intolerant PCOS with high metabolic risk. *Diabetes*. 2017;66(Suppl. 1):A563
- [94] Elkind-Hirsch KE, Paterson MS, Seidemann EL, Gutowski HC. Short-term therapy with combination dipeptidyl peptidase-4 inhibitor saxagliptin/metformin extended release (XR) is superior to saxagliptin or metformin XR monotherapy in prediabetic women with polycystic ovary syndrome: A single-blind, randomized, pilot study. *Fertility and Sterility*. 2017;107(1):253-260.e1. DOI: 10.1016/j.fertnstert.2016.09.023
- [95] Jensterle Sever M, Ferjan S, Janež A. DPP4 inhibitor sitagliptin in combination with metformin prevent weight regain in obese women with PCOS previously treated with liraglutide. *Endocrine Reviews*. 2017;38(3 Suppl): OR 28-2. ISSN: 1945-7189 Available from: <http://www.endocrine.org/meetings/endo-annual-meetings/abstract-details?ID=30608>
- [96] Bariatric Surgery Guidelines and Recommendations [Internet]. American Society for Metabolic and Bariatric Surgery. Available from: <https://asmbs.org/resources/bariatric-surgery-guidelines-and-recommendations> [Accessed: Jul 29, 2017]
- [97] Morínigo R, Moizé V, Musri M, Lacy AM, Navarro S, Marín JL, et al. Glucagon-like peptide-1, peptide YY, hunger, and satiety after gastric bypass surgery in morbidly obese subjects. *The Journal of Clinical Endocrinology and Metabolism*. 2006;91(5):1735-1740. DOI: 10.1210/jc.2005-0904
- [98] Evans S, Pamuklar Z, Rosko J, Mahaney P, Jiang N, Park C, et al. Gastric bypass surgery restores meal stimulation of the anorexigenic gut hormones glucagon-like peptide-1 and peptide YY independently of caloric restriction. *Surgical Endoscopy*. 2012;26(4):1086-1094
- [99] Korner J, Bessler M, Cirilo LJ, Conwell IM, Daud A, Restuccia NL, et al. Effects of Roux-en-Y gastric bypass surgery on fasting and postprandial concentrations of plasma ghrelin, peptide YY, and insulin. *The Journal of Clinical Endocrinology and Metabolism*. 2005;90(1):359-365. DOI: 10.1210/jc.2004-1076
- [100] Korner J, Bessler M, Inabnet W, Taveras C, Holst JJ. Exaggerated GLP-1 and blunted GIP secretion are associated with Roux-en-Y gastric bypass but not adjustable gastric banding. *Surgery for Obesity and Related Diseases: Official Journal of the American Society for Bariatric Surgery*. 2007;3(6):597-601
- [101] Eid GM, Cottam DR, Velcu LM, Mattar SG, Korytkowski MT, Gosman G, et al. Effective treatment of polycystic ovarian syndrome with Roux-en-Y gastric bypass. *Surgery for Obesity and Related Diseases*. 2005;1(2):77-80. DOI: 10.1016/j.soard.2005.02.008
- [102] Jamal M, Gunay Y, Capper A, Eid A, Heitshusen D, Samuel I. Roux-en-Y gastric bypass ameliorates polycystic ovary syndrome and dramatically improves conception rates:

A 9-year analysis. *Surgery for Obesity and Related Diseases*. 2012;**8**(4):440-444. DOI: 10.1016/j.soard.2011.09.022

- [103] Stroh C, Hohmann U, Lehnert H, Manger T. PCO syndrome—Is it an indication for bariatric surgery? *Zentralblatt für Chirurgie*. 2008;**133**(6):608-610. DOI: 10.1055/s-2008-1076869
- [104] George K, Azeez H. Resolution of gynaecological issues after bariatric surgery — A retrospective analysis. *Obesity Surgery*. 2013;**23**(8):1043. DOI: 10.1007/s11695-013-0986-z