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Potential New Pharmacological Approaches in Obese Women with Polycystic Ovary Syndrome

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Abstract

Obesity is frequently present in women with polycystic ovary syndrome (PCOS). It aggravates the adverse features of the syndrome and increases the metabolic risk in this population. Weight management by lifestyle intervention often remains unsatisfactory and non-sustainable. In the present mini review we revised limited studies addressing the potential use of agents mediating through GLP-1 in PCOS. We reported that short-term intervention with long acting GLP-1 analogue liraglutide is associated with consistent BMI decrease in treatment naive obese women with PCOS and in those who had been previously poor responders to metformin and lifestyle modification. Metformin, a well-established therapy used in PCOS with high metabolic risk, was recognized as a mechanistically well-suited combination with liraglutide. Short-term intervention with liraglutide also improved eating behavior in obese PCOS. Furthermore, we discussed the potential association of genetic variability of GLP-1 receptor and inter-individual differences in response to liraglutide regarding weight reduction. In addition, we challenged the original concept related to the enhancement of GLP-1 mediated action through phosphodiesterase 4 (PDE 4) inhibitions as a new potential therapeutic target in obesity-related population. We concluded that GLP-1 mediated agents are promising treatment strategies in the management of obese PCOS. However, larger sample size studies with longer durations of treatment may be required to examine potential benefits of these medications in decreasing metabolic risk and improving reproductive outcome in obese PCOS.

Keywords: Obesity; Polycystic ovary syndrome; Monotherapy; Insulin

Mini Review

Obesity is not intrinsically associated with polycystic ovary syndrome (PCOS), yet the risk for obesity is up to 2.8 higher than in women without PCOS with the pooled estimated prevalence of around 50% [1]. The amount and distribution of fat is a major contributor to severity and expression of PCOS. [2,3]. Obese women demonstrate more severe gynecological abnormalities, clinical and biochemical androgen excess, glucose intolerance and insulin resistance when compared with normal weight or lean women with PCOS.

Even modest weight reduction of 5-10% is substantial for improvement of reproductive and metabolic profile of obese PCOS patients. [3,4] Furthermore, weight loss has beneficial effects on all cardiovascular risk factors. Recent clinical practice guidelines recommend lifestyle modification as the first line intervention in obese PCOS [5]. However, the treatment goals with lifestyle intervention are usually hardly achievable and non-sustainable in everyday life. New treatment options for weight reduction acting through glucagon-like peptide (GLP)-1 mediated effect should be considered in the patients who have not responded to lifestyle modification.

Liraglutide, long acting GLP-1 analogue with 97% homology to human GLP-1, in dose of 3 mg, was recently approved for weight management in many countries. It has a significant dose depending effect on weight loss in overweight type 2 diabetic patients and in non-diabetic overweight persons [6-9]. Its effect on body weight appears to be due to reduction in food intake, mainly by a direct hypothalamic effect of the hormone. It also delays gastric emptying partly due to a central action mediated via the autonomous nervous system. It is unique in its ability to regulate eating behaviour. Stimulation of mesolimbic GLP-1 receptor is sufficient to reduce hunger-driven feeding, the hedonic value of food and food-motivation [10]. In two studies liraglutide produced significant improvements in eating behaviour in obese patients with type 2 diabetes mellitus (T2DM). The effect was maintained throughout the 6 months after discontinuation of liraglutide. It significantly reduced the urge for fat intake [11,12]. Such improvement in eating behaviour induced by liraglutide has not been reported for other glucose-lowering agents.

The experiences with liraglutide use in obesity related to PCOS are still very limited. A small- randomized study proved that short-term 12 week combined treatment with liraglutide 1.2 mg QD s.c. alone or in combination with metformin 1000 mg BID was associated with significantly greater weight loss in obese women with PCOS who had been previously poor responders regarding weight reduction on lifestyle intervention and metformin when compared to metformin monotherapy. The reported mean weight losses were 6.5 kg with liraglutide plus metformin, 3.8 kg with liraglutide alone and 1.2 kg with metformin alone [13]. Furthermore, short-term treatment with liraglutide was associated with significantly greater weight loss in a subset of obese patients with newly diagnosed PCOS and higher metabolic risk profile when compared to metformin and lifestyle intervention [14]. Both study designs were conducted with low dose liraglutide 1.2 mg before high dose liraglutide 3 mg was approved as an anti-obesity drug. Adding metformin to liraglutide seems to enhance the therapeutic index of GLP-1 enabling the use of lower dose of liraglutide in combination treatment [15-19]. It was demonstrated that metformin added to low dose liraglutide 1.2 mg was superior to low

dose liraglutide 1.2 mg alone in reducing mean body weight after 12 weeks also in treatment naïve obese women with PCOS. Addition of metformin also increased the proportion of individuals achieving clinically meaningful ≥ 5% weight loss to almost 60% compared to about 40% of good responders in low dose liraglutide monotherapy. [15]. In another study that primarily investigated the potential impact of liraglutide on markers of liver fibrosis in PCOS, an average weight reduction of 3.0 kg, yet achieved with larger dosage of 1.8 mg QD s.c. in monotherapy, was observed in a 24 weeks [20]. In an observational study without fixed period of time of mean duration 27.8 weeks and without fixed doses of liraglutide ranging from 0.6 mg up to 1.8 mg QD about 60% of patients, combination of liraglutide and metformin was also associated with significant weight loss of 9 kg in a larger cohort of PCOS patients [21]. It was also reported that short-term liraglutide treatment improved the impaired eating behaviour with significant decrease in emotional eating and that this improvement correlated with weight loss in PCOS patients [22].

There are not many studies with short acting GLP-1 receptor agonist (RA) addressing obesity. The only report evaluating the effect of short instead of long acting GLP-1 RA in PCOS was a 24-week randomized study of exenatide demonstrated a mean weight loss of 3.2 kg with exenatide monotherapy, 6.0 with combination therapy with metformin and 1.6 kg with metformin alone [23]. 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.

Weight lowering potential of GLP-1 RAs varies between obese individuals. Some obese subjects respond well to weight lowering potential of GLP-1 RAs and some do not. The potential predictors of different inter-individual weight lowering response were not yet clearly identified. Some studies reported that obese subjects without T2DM and with higher body mass index (BMI) achieved greater reduction in body weight with GLP-1 RAs than those with history of T2DM and lower BMI [8,24]. Recognizing that the weight reducing effects of GLP-1 RAs are mediated through GLP-1 receptor its genetic variability could be hypothetically associated with the inter-individually different response to weight lowering potential of liraglutide in metabolically balanced and BMI matched obese population. It was demonstrated in one study that some GLP1-R polymorphisms were associated with inter-individual differences in response to liraglutide regarding weight reduction in phenotypically and metabolically homogeneous cohort of obese women with PCOS [25].

Less recognized and completely distinct regulatory mechanisms related to the enhancement of GLP-1 mediated action through the inhibition of phosphodiesterase (PDE) 4 has recently became a reasonable focus of a potential new anti-obesity and metabolic management. Roflumilast, the first drug specifically targeting PDE4, is well recognized as efficient anti-inflammatory treatment of chronic inflammatory diseases, primarily chronic obstructive pulmonary disease (COPD) [26]. Collaterally, the 12 months use of roflumilast in COPD was associated with a weight decrease of about 2 kg versus placebo. In addition, short-term use of roflumilast has shown positive metabolic effects on glucose homeostasis and weight reduction in newly diagnosed T2DM without COPD with mean weight change of about 2 kg versus placebo [27]. A 12-week pilot randomized study evaluated the efficacy of roflumilsat in obese PCOS population. It demonstrated that roflumilast 500 mcg QD in combination with metformin 1000 mg BID significantly reduced body weight in obese PCOS when compared to metformin monotherapy, primarily due to a loss of fat mass with the between treatment difference of about 5 kg [28]. The hypothesis behind weight decrease observed with roflumilast is based on the PDE4 regulation of signalling pathways linked to GLP-1 release. In experimental rodent model a single treatment with roflumilast enhanced plasma GLP-1 levels up to 2.5 –fold [29]. A direct comparison of short-term intervention with liraglutide and roflumilast addressing weight management was performed in PCOS related obesity. Both monotherapy with liraglutide and roflumilast ware associated with significant weight loss in obese PCOS when compared to metformin arm, liraglutide being superior to roflumilast. Reduction of body weight with liraglutide resulted also in improvement of body composition significantly reducing visceral adipose tissue [30].

In summary, the novel pharmacological treatment concept in obesity and obesity related conditions should focus on distinct regulatory mechanisms of energy homeostasis and eating behaviour. 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. Larger and longer randomized studies are needed to establish the metabolic, reproductive, and cardiovascular risk reduction and to assess the sustainability and safety profile of weight reduction achieved by these potential new treatment strategies.

References

1. Lim S, Davies M, Norman R, Moran L (2012) Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 6: 618-637.
2. Lass N, Kleber M, Winkel K, Wunsch R, Reinehr T (2011) Effect of lifestyle intervention on features of polycystic ovarian syndrome, metabolic syndrome, and intima-media thickness in obese adolescent girls. J Clin Endocrinol Metab 11: 3533-3540.
3. Crosignani P (2003) Overweight and obese anovulatory patients with polycystic ovaries: parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet. Hum Reprod 9: 1928-1932.
4. Thomson R, Buckley J, Noakes M, Clifton P, Norman R, et al. (2008) The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome. J Clin Endocrinol Metab 9: 3373-3380.
5. National Institute for Health and Clinical Excellence (2006) Obesity Guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children. National Institute for Health and Clinical Excellence: Guidance
6. Astrup A, Rossner S, Van Gaal L, Rissanen A, Niskanen L, et al. (2009) Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet 9701: 1606-1616.
7. Davies M, Bergenstal R, Bode B, Kushner R, Lewin A, et al. (2015) Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes. JAMA 7: 687-689.
8. Vilsboll T, Christensen M, Junker A, Knop F, Gluud L (2012) Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ 344: d7771.
9. Wilding J, Overgaard R, Jacobsen L, Jensen C, le Roux C (2016) Exposure-response analyses of liraglutide 3.0 mg for weight management. Diabetes Obes Metab 5: 491-499.
10. Skibicka K (2013) The central GLP-1: Implications for food and drug reward. Front Neurosci 7: 181.
11. Keskitalo K, Tuorila H, Spector TD, Cherkas LF, Knaapila A, et al. (2008) The Three-Factor Eating Questionnaire, body mass index, and responses

to sweet and salty fatty foods: a twin study of genetic and environmental associations. Am J Clin Nutr 88: 263–271.

12. Inoue K, Maeda N, Kashine S, Fujishima Y, Kozawa J, et al. (2011) Short-term effects of liraglutide on visceral fat adiposity, appetite, and food preference: a pilot study of obese Japanese patients with type 2 diabetes. Cardiovasc Diabetol 1: 109.
13. Jensterle Sever M, Kocjan T, Pfeifer M, Kravos N, Janez A (2014) 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. EJE 3: 451-459.
14. Jensterle M, Kravos NA, Pfeifer M, Kocjan T, Janez A (2015) 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 14: 81-90.
15. Jensterle M, Goricar K, Janez A (2016) Metformin as an initial adjunct to low-dose liraglutide enhances the weight-decreasing potential of liraglutide in obese polycystic ovary syndrome: Randomized control study. Exp Ther Med 4: 1194-1200.
16. Maida A, Lamont B, Cao X, Drucker D (2011) Metformin regulates the incretin receptor axis via a pathway dependent on peroxisome proliferator-activated receptor-α in mice. Diabetologia 2: 339-349.
17. Mannucci E, Ognibene A, Cremasco F, Bardini G, Mencucci A, et al. (2001) Effect of metformin on glucagon-like peptide 1 (GLP-1) and leptin levels in obese nondiabetic subjects. Diabetes Care. 3: 489-494.
18. Mannucci E, Tesi F, Bardini G, Ognibene A, Petracca MG, et al. (2004) Effects of metformin on glucagon-like peptide-1 levels in obese patients with and without Type 2 diabetes. Diabetes Nutr Metab 17: 336-342.
19. Yasuda N, Inoue T, Nagakura T, Yamazaki K, Kira K, et al. (2002) Enhanced secretion of glucagon-like peptide 1 by biguanide compounds. Biochem Biophys Res Commun 5: 779-784.
20. Kahal H, Abouda G, Rigby A, Coady A, Kilpatrick E, et al. (2014) Glucagon-like peptide-1 analogue, liraglutide, improves liver fibrosis markers in obese women with polycystic ovary syndrome and nonalcoholic fatty liver disease. Clin Endocrinol. 4: 523-528.
21. Rasmussen CLS (2014) The effect of liraglutide on weight loss in women with polycystic ovary syndrome: An observational study. Front Endocrinol 5: 140.
22. Jensterle M, Kocjan T, Kravos N, Pfeifer M, Janez A (2015) Short-term intervention with liraglutide improved eating behavior in obese women with polycystic ovary syndrome. Endocr Res 3: 133-138.
23. Elkind-Hirsch K, Marrioneaux O, Bhushan M, Vernor D, Bhushan R (2008) Comparison of single and combined treatment with exenatide and metformin on menstrual cyclicity in overweight women with polycystic ovary syndrome. J Clin Endocrinol Metab 7: 2670-2678.
24. Niswender K, Pi-Sunyer X, Buse J, Jensen KH, Toft AD, et al. (2013) Weight change with liraglutide and comparator therapies: an analysis of seven phase 3 trials from the liraglutide diabetes development programme. Diabetes Obes Metab 15: 42-54.
25. Jensterle M, Pirs B, Goricar K, Dolzan V, Janez A (2015) 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. J Clin Endocrinol Pharm 7: 817-824.
26. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, Bundschuh DS, Brose M, et al. (2009) Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. Lancet 374: 695-703.
27. Wouters EF, Bredenbroker D, Teichmann P, Brose M, Rabe KF, et al. (2012) Effect of the phosphodiesterase 4 inhibitor roflumilast on glucose metabolism in patients with treatment-naive, newly diagnosed type 2 diabetes mellitus. J Clin Endocrinol Metab 97: 720-725.
28. Jensterle M, Kocjan T, Janez A (2014) Phosphodiesterase 4 inhibition as a potential new therapeutic target in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab 99: 1476–1481.
29. Vollert S, Kaessner N, Heuser A, Hanauer G, Dieckmann A, et al. (2012) The glucose-lowering effects of the PDE4 inhibitors roflumilast and roflumilast-N-oxide in db/db mice. Diabetologia 55: 2779–2788.
30. Jensterle M, Salamun V, Kocjan T, Vrtacnik Bokal E, Janez A (2015) 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. J Ovarian Res 8: 32.