Journal of Diabetes and Obesity

OMMEGA Publishers
Answering Intelligence

Mini Review Open Access

# 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 life style intervention often remains unsatisfactory and non-sustainable. In the present mini review, we revised limited studies addressing the potential use of agents mediating through glucagon-like peptide (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 life style 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 phosphordiesterase 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 out come in obese PCOS.

**Received date: November 27, 2016**
**Accepted date: February 06, 2017**
**Published date: February 10, 2017**

**Citation:** Janez, A. Potential New Pharmacological Approaches in Obese Women with Polycystic Ovary Syndrome. (2017) J J Diab Obes 4(1): 11- 13.

**DOI:** 10.15436/2376-0494.17.1246

## Introduction

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[1].

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 life style modification as the first line intervention in obese PCO[5]. However, the treatment goals with life style 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 life style 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 dependent effect on weight loss in overweight type 2 diabetic patients and in non-diabetic overweight persons[6-9]. Its anorectic effect appears to be due to reduction in food intake,

mediated secondary to its incretin effect that suppresses ghrelin releas[10]. 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 sc qd 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 mono therapy[13]. 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, achieved with larger dosage of 1.8 mg sc qd in monotherapy, was observed over 24 week[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 in 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 acting GLP-1 RA in PCOS was a 24-week randomized study demonstrated a mean weight loss of 3.2 kg with exenatide monotherapy, 6.0 kg with exenatide in adjunct to 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[13,23].

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, 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 and primarily chronic obstructive pulmonary disease (COPD)[26]. Collaterally, 12 months use of roflumilast in COPD was associated with a weight decrease of about 2 kg versus placebo[26]. 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 approximately 2 kg versus placebo[27]. A 12-week pilot randomized study evaluated the efficacy of roflumilast in an 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[29]. 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[30]. 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[30]. Reduction of body weight with liraglutide resulted also in improvement of body composition significantly reducing visceral adipose tissue[30].

In summary, novel pharmacological treatment 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 metabolic, reproductive, and cardiovascular risk

reduction and assess sustainability and safety profile of weight reduction achieved by these potential new treatment strategies.

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