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Overview of the Role of Glucagon like Peptide-1 Receptor Agonists in the Management of Polycystic Ovary Syndrome

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects premenopausal women. It is a multifactorial disease that involves hyperandrogenism, ovulatory dysfunction, insulin resistance and genetic factors. Women with PCOS present with menstrual disorder, hirsutism, and obesity. Diagnosis of PCOS involves evidence of ovulation dysfunction, hyperandrogenism, either physical or biochemical, and ultrasonographic evaluation of the ovarian morphology. There is no single treatment for PCOS but rather it is a symptom-oriented management. Glucagon-like-peptide-1 receptor agonists (GLP-1 RAs) are insulin sensitizers usually involved in the management of PCOS.
Aim: This article aims to review the evidence regarding the role GLP-1 RAs in the management of polycystic ovary syndrome.
Conclusion: GLP-1 RAs found to improve PCOS outcomes in the form of increasing menstrual frequency, reducing androgens levels, higher pregnancy rates, weight reduction, and improving insulin resistance. Mild and transient adverse events were observed such as nausea, diarrhea, headache, insomnia and mild hypoglycemic events. However, long term studies are required to assess long term effect of GLP-1 RAs and its safety during pregnancy.

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1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous and heritable condition that characterized by androgen excess, menstrual dysfunction and ovulation dysfunction with a variable clinical presentation [1,2]. It represents the single most common endocrine-metabolic disorder in reproductive-aged women that starts as early as menarche [3]. It affects from 5.5% to 19.9% of premenopausal woman worldwide based on 2003 Rotterdam criteria [4]. Prevalence of PCOS varies according to diagnosis criteria applied and the variable sensitivity of tests used within each criterion [4,5]. Endocrine aberrations found in PCOS are prolonged elevation of luteinizing hormone (LH) and Insulin resistance (IR) that leads to increase risk for diabetes mellitus (DM), obesity, high blood pressure and cardiovascular disease [6,7]. PCOS was assumed to be caused by a malfunction in pituitary gonadotropin secretion; however, primary functional ovarian hyperandrogenism is now thought to be the core defect in PCOS. Other factors that may be involved in the pathogenesis of PCOS are chronic inflammation, environmental exposure during in-utero life and genetic factors [7].

Patient with PCOS usually present with abnormal menstruation in form of oligomenorrhea, secondary amenorrhea, dysfunctional uterine bleeding or subfertility\infertility. Androgen excess manifests as hirsutism, voice deepening and increased muscle mass. Women with PCOS are at high risk for; subfertility and obstetric complications such as endometrial atypia or carcinoma, possibly ovarian malignancy, mood and psychosexual disorders, glucose intolerance and type 2 diabetes mellitus, hepatic steatosis metabolic syndrome, hypertension, dyslipidemia, vascular thrombosis, cerebrovascular accidents, and possibly cardiovascular events [8]. Almost half of women with PCOS are obese, thus, they need to be evaluated for their body mass index (BMI), lipid profile and blood pressure to estimate their cardiovascular risk as recommended by Royal college of obstetricians and gynecologists (RCOG) [9]. Screening of DM among PCOS patients by measuring fasting glucose level and oral glucose tolerance test is reasonable as diabetes found in approximately 10% of PCOS patients [10].

There is no an unequivocal test to diagnosis PCOS, yet it depends on the presence of ovulation dysfunction, hyperandrogenism, either physical or biochemical, and ultrasonographic evaluation of the ovarian morphology. Exclusion of thyroid disorder, prolactin elevated level and Congenital adrenal hyperplasia is advised during the process of PCOS diagnosis [11]. Therapeutic decisions in PCOS depend on the patients' phenotype, concerns, and goals, and should starts initially with lifestyle modification in form of weight reduction by diet control, regular exercise and behavioral changes [12]. Other treatment options focus on improving fertility status, suppression and counteracting androgen secretion and action and management of comorbidities associated with PCOS [12,13]. Incretins namely Glucagon like peptide (GLP) and insulinotropic peptide (GIP) are hormones produced by enteroendocrine cells which lead to increase insulin level as a response to food ingestion. Glucagon like peptide receptor agonists (GLP-1 RAs) are incretin mimetics that commonly used in the management of DM and recently has been introduced for PCOS management [1]. GLP-1 RAs act by increasing the level of GLP-1 hormone, enhancing insulin secretion as well as decreasing glucagon release and it slows stomach emptying leading to early satiety [14]. Thus, GLP-1 RAs may provide a promising opportunity for weight control and glycemic control in a monotherapy option. The aim of this review to summarize the evidence in the literature about the role of GLP-1 RAs in the management of PCOS.

2. GLUCAGON-LIKE-PEPTIDE-1 RECEPTOR AGONISTS AND FEMALE REPRODUCTIVE SYSTEM

Irregular menstruation appears to be one of the first symptoms of ovulatory dysfunction indicating an early sign of infertility [15]. Forty-two women with PCOS and ovulatory dysfunction were randomized either to exenatide alone, metformin alone or both medications for 24 weeks. Besides significant weight reduction, improved menstrual frequency and ovulation rate were observed in both groups with a higher rate of improvement experienced in the combination group (84%), whereas 29% and 50% improvement experienced in metformin and exenatide groups respectively [16]. However, few studies resulted in no change regarding menstrual frequency after liraglutide in PCOS patients despite significant

weight loss that could be attributed to variable liraglutide dosing, short-term trials, or low sample size [17]. Full mechanism of restoring menstrual regularity in PCOS patients still not sufficiently studied and it needs further studies in the future.

Weight reduction is encouraged by international guideline either before natural conception or before in-vitro fertilization (IVF) [18]. Weight loss by diet and exercise has resulted in a higher pregnancy rate among obese women [19]. A study conducted in 2018 by Salamun et al., they compared between intervening with metformin alone versus combination of liraglutide and metformin in obese patients with PCOS and attempting for first or second IVF for 12 weeks. In addition to significant weight reduction in both interventions irrespective of treatment employed, they concluded that preconception combination therapy is superior to preconception treatment with metformin in regards to increase pregnancy rates [20].

Liraglutide for 26 weeks in overweight PCOS patients compared to placebo has resulted in improved insulin sensitivity and improved ovarian function in form of decreased Free testosterone level, increased Sex Hormone Binding Globulin (SHBG), enhanced uterine bleeding pattern and interestingly, reduced ovarian volume [21]. This is may be attributed to improved insulin sensitivity as PCOS patients experience improved menstrual frequency after weight loss and decreased fasting insulin levels in contrary to women with persistent obesity [22]. That's added to the fact that PCOS patients experience improved menstrual frequency after metformin therapy in both obese and normal weight patient [23]. Ovarian volume was associated with androgen level [24], thereby decreased ovarian volume in this study could be explained by decreased androgen level. Regarding Anti-Mullerian hormone (AMH), they noticed a trend of decreased AMH among patients who received liraglutide. Decreased level of AMH was noticed in association with weight reduction and improved menstrual frequency [21].

Leptin level found to be high in patients with PCOS leading to decreased the expression of aromatase mRNA in the ovarian granulosa cells that lead to cellular apoptosis. Few studies suggested that GLP-1 RAs improve the oocyte maturation partially via enhancing the ovarian granulosa cells activity [25,26].

Another study conducted in 2015 by Jensterle et al., they recruited 32 women who was recently diagnosed with PCOS. They were randomized to metformin 1g or liraglutide 1.2 mg subcutaneously. There was a significant weight loss among all patients irrelevant to medication received. Regarding endocrine changes, there was a significant difference of LH level between two groups. In subjects received metformin, LH was decreased, while in subjects who received liraglutide they had a significant LH level elevation. Additionally, testosterone level was decreased in patients who received metformin with no significant alteration of testosterone level in patients who received liraglutide [27].

3. GLUCAGON-LIKE-PEPTIDE RECEPTOR AGONISTS AND OBESITY

Almost two thirds of PCOS patients are obese and a weight reduction by 5-10% appears to enhance reproductive and metabolic outcomes in women with PCOS [28,29]. When GLP-1 RAs bind to different receptors in the hypothalamus, it results in decreased appetite, slow gastric motility, and early satiety [30]. Weight loss associated with GLP-1 RAs is mediated by central mechanism via direct suppressing effect on the feeding center resulting in eating behavioral changes [31].

In a clinical trial conducted between 2011 to 2012 by Sever et al., they recruited 40 women with PCOS and obesity with previous treatment with metformin for six months and failed to lose > 5% of their weight. They were randomized to 1 out of 3 groups: Metformin only 1000 mg (group A), combination between metformin and subcutaneous liraglutide 1.2mg (group B) or subcutaneous liraglutide 1.2mg QD alone (group C) for 3 months. The main outcome was weight reduction. Among all three groups BMI has significantly decreased. Total of 38% of study subjects lost ≥ 5% of weight in 12 weeks, 22% of them were in group B and 16% were in group C. The highest weight reduction was achieved at the last 4 weeks of the treatment. Significant reduction of waist circumference was noted among subjects of group B followed by group C and group A. A total of 33% of study subjects had impaired glucose tolerance, 42% of them had normal glucose after 12 weeks of the beginning of the treatment. At the start of treatment, six patients of group A, four of group B and seven of group C had metabolic syndrome [32].

Seventy-two PCOS overweight patients experienced a significant weight reduction by 5.6% of their baseline weight, decreased hepatic fat composition by 44%, loss of 18% of visceral adipose tissue, and reduction of Non-alcoholic fatty liver disease prevalence rate almost by to thirds after liraglutide for 26 weeks when compared to placebo treatment [33].

Another study conducted in 2017 by Jensterle, 28 women completed a clinical trial and randomized to either liraglutide 3mg as a monotherapy or combination of metformin 1g and liraglutide 1.2 mg for 3 months. A significant weight reduction was observed in both regimens with a higher weight reduction noted with higher doses of liraglutide [34].

Weigh regain after liraglutide cessation is quite common. In a study conducted in 2017, they recruited 24 obese PCOS patients who had been treated previously by liraglutide for weight loss and randomized either to monotherapy of metformin 1g or metformin 1g combined with sitagliptin 100mg for 12 weeks. The main outcome was to prevent weight regain after liraglutide treatment. Combination group experienced a significant weight maintenance whereas metformin group had a significant weight regain. No further weight reduction was noticed in either group [35].

4. GLUCAGON-LIKE-PEPTIDE RECEPTOR AGONISTS AND GLUCOSE HEMOSTASIS

Approximately 40% to 60% of PCOS patients suffer from hyperinsulinemia and IR [36]. Besides that, incretin disorder found to be a contributing factor of PCOS pathophysiology [37], thus including GLP-1 RAs in the management of PCOS is logical. However, GLP-1 RAs do not act directly on insulin secretion, but it rather improves insulin insensitivity via significant BMI reduction effect, appetite inhibition, inducing early satiety [38], and slowing gastrointestinal tract motility [39]. Additionally, it inhibits lipogenesis, stimulates lipolysis and it suppresses the inflammatory process by decreasing macrophages invasion to improve insulin insensitivity of the fat, hepatic, and muscle tissues. It acts on the liver by decreasing the very low-density lipoprotein production by hepatic cells [40]. Inflammation of adipose tissue plays a crucial role in the pathophysiology of IR in obese individuals. According to Guo C et al., they suggest that GLP-1 RAs act on IR by inhibiting the inflammatory process of the adipose tissue Additionally, it enhances insulin secretions by binding with GLP-1 receptors of the pancreatic beta-cell resulting in a change of molecular pathways in order to secrete insulin as well as stimulate expansion and proliferation of pancreatic beta cells [41].

Improved glycemic control in PCOS patients in form of decreased fasting blood glucose and Hemoglobin A1C (HbA1C%) were observed in liraglutide group when compared to placebo group [33]. Insulin resistance and glucagon levels remain unaltered in either group. Available data suggests liraglutide is not as metformin in respect to improve insulin sensitivity [35].

Regarding metabolic syndrome, combination between metformin and liraglutide has resulted in resolution of metabolic syndrome in PCOS patients, whereas no difference noted in monotherapy with either metformin or liraglutide [32].

Generally, GLP-RAs were well tolerated by patients with mild and transient side effects [29]. Adverse events observed in patient taking liraglutide are nausea, vomiting, constipation, diarrhea, gall bladder stone related pain, mild hypoglycemia, and headache with nausea being the most frequent adverse event [20,25,34,35,41].

5. CONCLUSION

In conclusion, the available data suggests GLP-1 RAs are promising therapeutic option for PCOS. It enhances ovarian function by improving menstrual frequency, decreasing free testosterone level, increasing SHBG, and decreasing ovarian stromal volume. A higher rate of pregnancy rate per embryo transfer observed after a pre-conceptional intervention with liraglutide in patients attempting IVF. Regarding LH, higher levels observed after liraglutide treatment. Weight loss by >5% and decreased waist circumference accomplished by short term treatment with GLP-1 RAs as well as decrease visceral fatty tissues and non-alcoholic fatty liver disease. Weight reduction rate higher with higher doses of GLP-1 RAs and when combine with metformin. Regarding glucose hemostasis, intervention with GLP-RAs resulted in decrease fasting insulin level, improved HbA1C% and improve blood sugar readings. Patients with PCOS experienced mild and temporary adverse events such as nausea, vomiting, and minor

hypoglycemic events. Longitudinal studies are recommended in order to investigate the long-term consequences of GLP-1 RAs in PCOS patients as well as its safety during pregnancy.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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