Review Article

Glucagon-like peptide 1receptor agonists for the treatment of Polycystic Ovary Syndrome: A systematic review and meta-analysis of randomized controlled trials

Abstract

Background: Since the Polycystic Ovary Syndrome (PCOS) phenotype might change at different points in a person's life, individualized diagnosis and treatment are required. Since glucagon-like peptide 1 (GLP-1) receptor agonists (RA) improve insulin sensitivity and reduce the risk of cardiovascular disease, they offer a unique opportunity to treat many comorbid diseases and phenotypic aspects of (PCOS) all at once.

Method: The PICO framework—which includes the terms "participants," "intervention," "control," and "outcome"—formed the basis for the search parameters. The appropriate research publications were identified by searching many databases, including Web of Sciences, PubMed, Scopus and PRISMA flow chart was constructed. RevMan 5.4 was utilized for the meta-analysis, while RoB-2.0 was employed for quality control.

Results: After following PRISMA, 14 research articles were included in the present systematic review and meta-analysis. GLP-1 RAs alone or in combination gave good results when compared with control/placebo/other drugs. In the meta-analysis, GLP-1 RA

was compared to control (Metformin, a comparative drug, a placebo, and other treatments)for Menestral frequency rate (MFR), Free Androgen Index (FAI), Homeostasis Model Assessment-estimated Insulin Resistance (HOMA-IR), and Total Testosterone (Total T). The results showed that GLP-1 RA had a statistically significant effect on MFR and Total T, indicating that the intervention was more effective than the control group but had no effect on FAI and HOMA-IR, suggesting that both GLP-1 RA and the control group were equally effective. When the quality assessment was done, 7 studies had low risk of bias, and 7 had some concerns, while no study had a high risk of bias. **Conclusion:**GLP-1 RAs may be suitable for obese patients with PCOS, particularly those with insulin resistance. However, as 7 studies had questions about randomization. There has to be more high-quality studies conducted on GLP-1 RAs to determine their effectiveness for PCOS in women.

Keywords: Insulin resistance, Insulin sensitivity, obesity, overweight, PCOS

Introduction

For women, polycystic ovarian syndrome (PCOS) is the most prevalent endocrine disease [1], andit affects 6-20% of women of reproductive age [2]. Many women of childbearing

age suffer from PCOS, which is marked by ovulatory failure, hyperandrogenism, and metabolic dysfunction [3].In addition, PCOS symptoms other than those related to reproduction include chronic low-grade inflammation and resistance to insulin[4]. Similarly, excess luteinizing hormone (LH) and a relative lack of follicle-stimulating hormone (FSH), which promote the generation of too much testosterone and ovulatory dysfunction, are also thought to be the causes of PCOS [5]. It is advised to treat PCOS with a customized strategy based on unique manifestations because the disorder has a complex clinical presentation and affects numerous organ systems [6].The PCOS phenotype can alter across different life phases, necessitating a customized approach to diagnosis and therapy [7]. Therefore, symptomatic therapy primarily involves menstrual cycle control, weight management, anti-hyperandrogenaemia therapy, and the management of metabolic diseases associated with insulin resistance [8] is advised. In addition, some PCOS recommendations presently prescribe metformin as a second-line treatment because it is a powerful insulin sensitizer [8] and lifestyle changes, which will help the patient lose weight and regain their reproductive and metabolic health [9].Similarly, combined oral contraceptives, inositol and anti-androgen medications are among the therapeutic pharmacological options for non-infertility indications, addressing various clinical manifestations of PCOS, according to the international evidence-based guideline for assessing and managing PCOS published in 2018 [10]. Recent research has revealed

promising new treatments for PCOS, such as novel insulin sensitizers to treat peripheral metabolic dysfunction, androgen excess treatment with pharmaceuticals, central neuroendocrine dysregulation treatment with kisspeptin signaling modulation [11].

A hormone called glucagon-like peptide 1 (GLP-1) is produced when intestinal epithelial endocrine L-cells process proglucagon. GLP-1 is the primary incretin hormone in healthy people [12]. Due to the existence of GLP-1 Receptor Agonistics (RAs), there is a rare chance to treat both hyperglycemia and excess body weight at the same time. GLP-1 RAs are a class of drugs with incretin-mimicking properties authorized for treating type 2 diabetes[13]. In addition,GLP-1-RA presents a rare opportunity to simultaneously treat a number of coexisting conditions and phenotypic manifestations of PCOS, as these medications enhance insulin sensitivity, lower the risk of cardiovascular disease (CVD)[14], cause weight loss as well as insulin resistance[15], and ameliorate nonalcoholic fatty liver disease[14].When administered alone or with metformin, Exenatide and Liraglutide are effective treatments for PCOS. When creating treatment plans for PCOS women with accompanying risk factors, and are looking for treatment for infertility, GLP-1 RAs should be given specific consideration [14]. Additionally, some GLP-1 RAs can be used once a week and do not result in hypoglycemia[16]. Given that up to 80% of PCOS-affected women are overweight or obese and that about 70% of afflicted women are insulin resistant, these effects have provided a rare opportunity to address many PCOS

symptoms simultaneously[17]. Using GLP-1 RAs as monotherapy or in combination with metformin, recent small, short-term studies in obese PCOS women revealed promising outcomes in terms of weight loss and a drop in testosterone levels[18].The efficacy and safety of GLP-1 RA and metformin in the treatment of women with PCOS have been compared in randomized controlled trials (RCTs) [19, 20]. The findings indicated that GLP-1 RAs outperformed metformin in their ability to help PCOS patients lose weight. However, another study observed that the weight loss result in a GLP-1 RA and metformin combination was comparable to the weight loss effect in PCOS patients receiving metformin as a single therapy [21]. Meanwhile, GLP-1 RAs were also found to be successful in controlling menstrual periods in adolescent PCOS patients [22].

Although the effectiveness of GLP-1 RAs in treating PCOS patients has also been the subject of multiple studies, but more recent research is needed to determine its efficacy and safety. In addition, the research findings were varied since their sample sizes were small and their degrees of quality varied. To give physicians treating PCOS evidence-based treatment options, the current study used a systematic review and meta-analysis of the available literature to assess the efficacy and safety of GLP-1 RAs used in women with PCOS.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria were followed in conducting this systematic review and meta-analysis[23].

Literature search

The search strategy was established according to the participants, intervention, comparators or controls, and outcome (PICO) framework [24]. Population / Participants: This review included humans with PCOS. Intervention: Efficacy of GLP-1 RAs against the PCOS. Comparison: Other treatment or control groups used for PCOS. Outcomes: Updated systematic review and meta-analysis of the literature on efficacy and safety of GLP-1 RAs. Different databases such as Web of Sciences, PubMed, and Scopus were searched for the relevant research articles using different keywords such as Glucagon-like peptide 1 receptor agonist, GLP-1, polycystic ovary syndrome, PCOS, Exenatide, Liraglutide, Dulaglutide, Semaglutide, metformin, dimethylbiguanide, and other medications' MeSH terms were used, as well as combinations of those terms. The search only included literature published up to date based on human RCTs.

Inclusion criteria

Articles focused on the efficacy of GLP-1 RAs; studies followed RCTs research design, only humans as study test subjects, participants with no age limit, and only English-published articles were included.

Exclusion criteria

Studies without control or comparison groups, non-English articles, studies other than RCTs, and studies that used animals as test subjects were excluded.

Study selection and assessment

There was an independent evaluation of the original publications, study titles, and abstracts. Two reviewers independently evaluated the entire texts of papers that met the inclusion requirements, and their conclusions were discussed to come to a consensus. Any disagreements was handled with the third independent reviewer and settled through consensus if there were any.

Data extraction

Data extraction was done on the shortlisted studies that matched the requirements for inclusion. A data extraction form was used to record the data that was extracted after screening the paper's title, abstract, and full text. Two reviewers independently record each study's authors, year of publication, mean age, BMI, country, sample size, efficacy, safety profile (adverse events), findings, conclusion, and limitations for a systematic review. While for the meta-analysis: total participants, participants in the GLP-1 RA group, and participants in the control group, along with efficacy data interms of menstrual frequencies, total serum testosterone concentration, Free androgen index(FAI), and HOMA-IR.

Quality assessment

Robvis was utilized in RCTs with Risk of Bias-2 (RoB-2) [25]. RoB 2 is categorized into a preset set of bias domains, focusing on a variety of trial design, conduct, and reporting aspects. Within each domain, a series of "signaling questions" questions aims to extract information about trial characteristics that are crucial to the risk of bias.

Data analysis

The included articles in the systematic review was compiled utilizing qualitative analysis. The PRISMA checklist was utilized to conduct a systematic review of pertinent literature, and a step-by-step method for choosing articles were also be provided. While, meta-analysis was performed using RevMan 5.4[26] to calculate the Cochrane Q and I^2 values, which quantify trial dispersion. The random effects model was used, with the significance level set at 0.05.

Results

Literature searched

All of the research were published in reputable academic journals, and a total of 1485 articles were found after searching the literature using certain online databases. However, 75 of the duplicates had to be removed. After eliminating duplicates, 1410 publications had their titles and abstracts combed over; 1378 were eventually axed for being irrelevant to

our study. A total of 32 papers were assessed extensively, and 18 were eventually removed (Figure 1). The most salient features of the 14 research articles published between 2008 and 2022 are summarized.

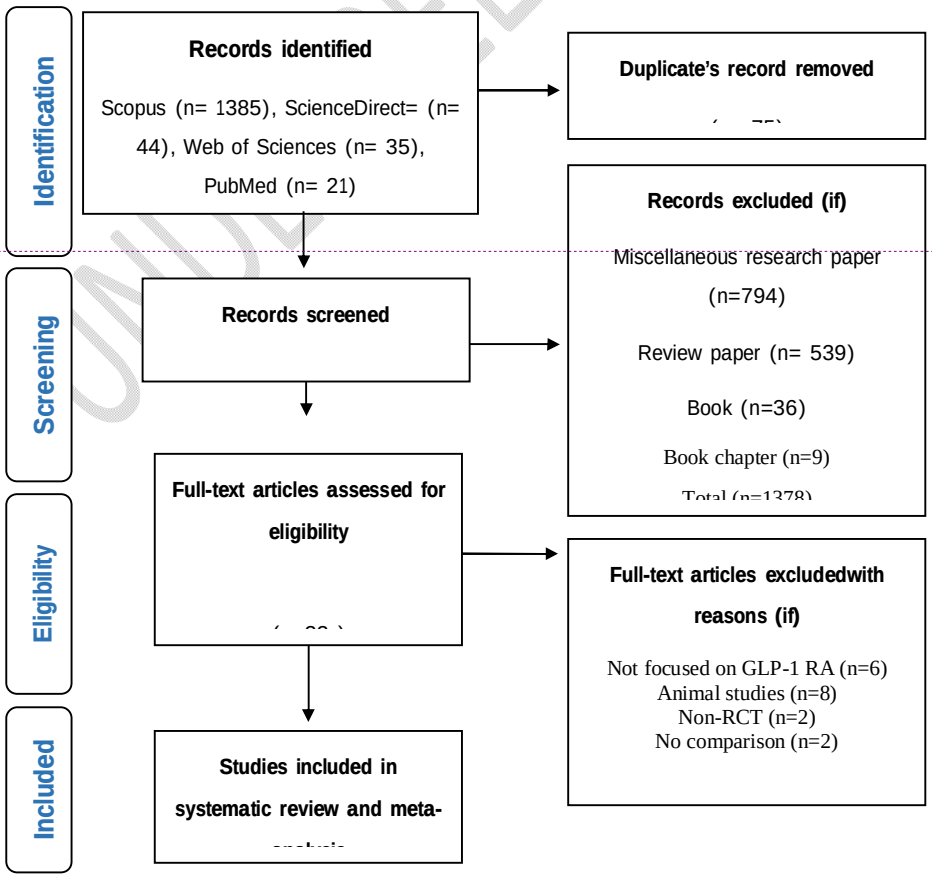

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Figure1. Flow chart of studies search and the articles selection process according to PRISMA guidelines.

General characteristics

Most of the studies were reported from China [15, 20, 27-29], followed by Slovenia [21, 30-32], USA [19, 33, 34] and Denmark [35, 36]. Maximum participants (176) were included in a conducted by Liu, Zhang [27], while a minimum of 27 participants were included by Salamun, Jensterle [21]. In the present systematic review, young participants were included as indicated in Table 1. Meanwhile, 11 studies used GLP-1 RA (Exenatide and Liraglutide) as a monotherapy, while 3 studies used as a combo with Metformin and clomifene citrate. Additionally, the dose for GLP-1 RA was 10 µg to 3 mg; for the comparison

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group metformin (1000-2000 mg), for DAPA and placebo dose was 1.8 mg-3mg (Table 1). The treatment duration was 12 weeks to 32 weeks, as stated in Table 1. Similarly, a significant BMI reduction can be seen after the treatment (Table 1). Meanwhile, in the camparison group there was a reduction in the BMI but not significant compared to the GLP-1 RA group. Maximum reduction of BMI was seen in the study conducted by Liu, Zhang [27], and the remaining values are stated in Table 1.

Table 1. General characteristics of included studies.

Reference	Country	N	Mean age (Mean±SD)	Intervention group baseline			Intervention group after therapy	Comparison group baseline			Comparison group after therapy
				Intervention/N	Dose/ wks	BMI (Mean ±SD)	BMI (Mean±SD)	Control Intervention/N	Dose (mg)	BMI (Mean±SD)	BMI (Mean±SD)
[19]	USA	40	28.2±1.1	Exenatide/14	10 µg bid (24 wks)	40.3±2	39.3±2	Metformin/14	1000	43.3±2	42.3±2
[30]	Slovenia	45	30.7 ± 7.9	Liraglutide/14	1.2 mg (12 wks)	36.7 ± 5.6	35.6 ± 5.8	Metformin/13	1000	39.4 ± 6.9	39.3 ± 7.0
[31]	Slovenia	44	30.3±.4.4	Liraglutide/21	1.2 mg (12 wks)	36.7±5.1	35.3±5.1	Metformin+ Liraglutide/22	1000+1.2	37.7±4.0	35.5±4.2
[32]	Slovenia	28	33.1 ± 6.1	liraglutide/14	3mg (12 wks)	39.2 ± 5.5	37.0 ± 5.5	Metformin+ Liraglutide/14	2000+1.2	37.5 ± 5.3	36.2 ± 5.5
[27]	China	176	27.93±2.70 EX, 27.69±3.80 MET	Exenatide/78	10 µg/12 wks	29.16± 3.11	26.04±3.52	Metformin/80	1000	28.29±1.86	27.20±1.80
[35]	Denmark	72	31.4 lIRA, 26.2 placbo	Liraglutide/48	1.8 mg (26 wks)	Unclear	Unclear	Placebo	Unclear	Unclear	Unclear
[28]	China	88	25.75 ± 6.33	Exenatide+clomifene citrate/45	10 µg+50 mg/12 wks	26.26 ± 5.71	NA	Meformin/33	2000	25.74 ± 6.37	NA
[20]	China	82	27.70 ± 3.41 EXE, 28.16 ± 3.92 MET	Exenatide/31	10 mg/12 wks	28.27 ± 4.85	26.12 ± 5.18	Metformin/32	1000	28.66 ± 4.61	27.27 ± 4.13
[36]	Denmark	72	NA	Liraglutide/48	1.8 mg/26 wks	Unclear	Unclear	Placebo/24	1.8	Unclear	Unclear
[21]	Slovenia	27	31.07±4.75	Liraglutide+Metformin/12	1.2mg+1000mg/12 wks	37.8±3.0	35.1±3.5	Metformin/11	1000	35.5±4.9	33.0±3.3
[33]	USA	119	18–45	Exenatide/20	2mg (24 wks)	38.6 ± 1.1	37.3 ± 1.1	DAPA+Metformin/19	10+2000	37.6 ± 1.1	37 ± 1.2
[15]	China	50	30.10 ± 4.52 COM, 28.17 ±	Exenatide+Metformin/19	2mg+500mg (12 wks)	30.80 ± 3.41	29.40 ± 3.32	Metformin/21	500	30.40 ± 3.16	29.63 ± 2.80

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[29]	China	150	18-45	Exenatide/50	20µg (12 wks)	30.99	28.46	Metformin/50	2000	29.64	28.19
[34]	USA	82	18–45	Liraglutide/55	3mg (32 wks)	41.6±1.1	39.1 ±1.1	Placebo/27	3	43.9±1.7	43.4 ±1.8

Abbreviations:N=Total number; NA=Not Available; BMI= Body Mass Index; Wks= Weeks; SD=Standard Deviation; DAPA=Dapagliflozin

Adverse events

All studies reported nausea as the primary adverse event in both intervention and comparison groups. Meanwhile, other significant adverse events such as headache, diarrhoea and vomiting were also reported by most of the studies. The remaining adverse events are presented in Table 2.

Table 2. Adverse events occurred during the treatment.

Reference	Adverse events	
	Intervention	**Comparison**
[19]	Nausea, Cramping, vomiting, Headache, injection site pain, pregnancy, dysfunctional menstrual bleeding	Nausea, diarrhea, bloating, vomiting, stomachache, constipation, fatigue, pregnancy, menstrual cramps, dysfunctional menstrual bleeding, migraines, hot flashes
[30]	Nausea, obstipation, diarrhea, headache and insomnia	Diarrhea and nausea
[31]	Nausea	Nausea
[32]	Nausea	Nausea
[27]	GI discomfort, nausea, bloating, vomiting, dizziness and a rash	Nausea, diarrhea, bloating, vomiting, stomachache, and constipation
[35]	Gallstone-related pain, Nausea	Gallstone-related pain
[28]	Headache, vomiting, and nausea Hot flushes, hazy vision, breast soreness, stomach aches, weariness, and erythema are some of the symptoms of increased or irregular bleeding	Headache, vomiting, and nausea Hot flushes, hazy vision, breast soreness, stomach aches, weariness, and erythema are some of the symptoms of increased or irregular bleeding
[20]	Nausea, bloating, vomiting, GI spasm, dizziness, weakness, subcutaneous induration	Nausea, diarrhea, bloating, vomiting, GI spasm, stomachache, constipation
[36]	Nausea, constipation and Gallstone-	Nausea and Gallstone-related pain

	related pain	
[21]	Nausea and headache	Nausea and diarrhea
[33]	Nausea, irritation, rash, pregnancy	Nausea, upset stomach, yeast infection, UTI, frequent urination, stuffy nose
[15]	Nausea, diarrhea, bloating, vomiting, headache, constipation, fatigue, dizziness, urticaria, injection site pain and itchy, subcutaneous induration	Nausea, diarrhea, bloating, vomiting, headache, constipation, fatigue, dizziness, stomachache
[29]	Nausea, vomiting, headache, metallic taste and flushing	Nausea, vomiting, headache, metallic taste and flushing
[34]	Nausea	Nausea

Outcomes

Overall, GLP-1 RA (Exenatide and Liraglutide) had positive effects in terms of reducing weight, BMI, and CW when compared to the comparison group (Metformin or placebo)[20, 27, 29, 30, 34-36]. However, when GLP-1 RA was used in combination with metformin, its efficacy increased and gave better results in reducing insulin resistance in PCOS women[15, 19, 21, 28, 31, 33] while single study reported that monotherapy of GLP-1 RA gave better results then combination [32] as indicated in Table 3.

Table 3. Major outcomes of the included studies.

Reference	Outcomes	Conclusion	limitations
[19]	Intervention group: <BMI and belly fat, > free androgen index, and enhancing insulin sensitivity, and regulating menstrual cycles. Both interventions (Exenatide) arms were more successful than the comparison group (Metformin) in encouraging weight loss.	Combined combinantionof intervention and comparison group improves reproductive function, insulin-glucose parameters, and adiponectin in obese women with PCOS.	Small sample size
[30]	Liraglutide resulted in greater reductions in weight (p = 0.022), BMI (p = 0.020), and waist circumference (p = 0.007). The VAT area decreased (p = 0.015) and the OGTT glucose homeostasis dynamics improved.	Liraglutide was superior to metformin	Study design, treatment time
[31]	Combination (Liraglutide and Metformin) had a greater drop in BMI; 2.20.8 kg/m^2) compared to those treated with Liraglutide alone (1.41.2 kg/m^2) (P=0.024).	Combination was more effective than Liraglutide alone at lowering body weight in treatment-unexperienced obese PCOS patients.	Short observation period, sample size
[32]	Both combinations (Liraglutide and Metformin), weight loss was observed (p=0.002) and for Liraglutide in (p=0.001). However, Liraglutide had a higher reduction in BMI and waist circumference than a combination. In both treatments, the OGTT, glucose levels were significantly reduced. Significantly as well as total testosterone levels, were lowered.	Obese PCOS patients can lose weight with Liraglutide 3 mg. Nearly 60% of women given Liraglutide 3 mg lost at least 5% of their body weight in 12 weeks.	Short observation period, sample size
[27]	The Exenatide group lost considerably more weight (P<0.001) and fat percentage (P<0.001), had less insulin resistance (P<0.001), and had more menstrual frequency ratio (P<0.001).	Significant results in terms of weight loss and increase in pregnancy rates in overweight or obese women with PCOS	Poor long-term compliance
[35]	Compared to the placebo group, those on Liraglutide lost an extra 5.2 kilograms (P=0.0001). Liraglutide was associated with an improvement in the bleeding ratio compared to placebo (P=0.05), while the free testosterone level went down by 0.005 nmol/L.	Liraglutide intervention altered ovarian dysfunction in an overweight PCOS population	Selection bias, the bleeding pattern was assessed using menstrual bleedings rather than ovulations, type 2 error.
[28]	The observation group had significantly reduced HOMA-IR compared to the control group (P<0.05), and had significantly greater ovulation and pregnancy rate (P<0.05).	When used together, exenatide and clomifene citrate are effective treatments for PCOS	NA

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[20]	In terms of weight reduction, Exenatide treatment was more effective than Metformin treatment (P=0.009). While both treatments resulted in significant reductions in HOMA-IR (P<0.001. Both therapies resulted in a notable decrease in FAI. The frequency of menstruation did not change substantially (P > 0.05).	In terms of weight loss and insulin sensitivity, short-term exenatide therapy is more effective.	NA
[36]	Weight loss of 5.2 kg (5.6%) was seen with liraglutide treatment compared to placebo. Whereas measures of insulin resistance did not change.	Significant outcomes were seen in PCOS patients treated with Liraglutide for 26 weeks.	NA
[21]	Weight loss was similar between groups (Metformin and combination (Liraglutide+Metformin) (P=0.246). In contrast to the Metformin group (28.6% PR/ET), the combination group (85.7%) had considerably higher PR/ET (P=0.03). In the combination group, the 12-month cumulative PR was 69.2%, but in the Metformin group, it was just 35.7%.	Liraglutide and metformin in combination aresuperior in PCOS treatment.	Small sample size
[33]	Exenatide and combination (Exenatide and DAPA) led to reductions in BMI and WC, the combination led to more improvements in MBG, the Exenatide in SI, and IS. All medications resulted in decreases in fasting glucose, testosterone, fasting insulin, and blood pressure.	Combination (Exenatide and DAPA) was more effective than each component alone.	Lack of a placebo-only arm, study design, small sample size, absence of gold-standard measures of insulin sensitivity, serial assessments were made over only 24 weeks of treatment
[15]	The combination (Exenatide+Metformin) group dropped an average of 3.8±2.4 kg, whereas those in the Metformin group lost an average of 2.1±3.0 kg. Reductions in BMI and WC were larger in the combination group, than in the Metformin group.	Combination therapy resulted in greater weight reduction and an increase in insulin sensitivity in obese and overweight women with PCOS, with tolerable short-term adverse effects	NA
[29]	Higher levels of Exenatide were linked to better glucose control throughout the OGTT's second hour than Metformin	Exenatide increased postprandial insulin production, leading to a better percentage of prediabetes remission in PCOS patients than Metformin monotherapy	Single-center design, small sample size, short duration of treatment

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[34]	At week 32, those taking Liraglutide 3 mg were more likely to have lost at least 5% of their body weight compared to those taking placebo. Liraglutide considerably decreased FAI.	Liraglutide was superior than placebo for women with PCOS	The absence of gold-standard measures of insulin sensitivity, second-generation immunoassay was used for total T, the discontinuation rate, the occurrence of pregnancy during the program, short duration of study.

Abbreviations:BMI=Body Mass Index; PCOS=Polycystic Ovary Syndrome; VAT=Visceral Adipose Tissue;OGTT=Oral Glucose Tolerance Test; HOMA-IR=Homeostasis Model Assessment-estimated Insulin Resistance; FAI=Free Androgen Index; PR=Partial clinical Remission; ET=Endometrial Thickness; DAPA=Dapagliflozin:WC=Weist Circumference;WBG=Whole blood Glucose.

Meta-analysis (Sub-group analysis)

Sub-group analysis was performed to see the association between intervention and comparison groups (Figure 2). There were four sub-groups (MFR, FAI, HOMA-IR and Total T).The pooled results for MFR for both intervention and comparison groups were reported by 4 researchers, with significant heterogeneity between them (I^2 = 100%, P<0.000001). A random-effects model was used to combine the results. There was a substantial difference and association between the intervention and comparison group in terms of MFR, as shownin Figure 2 [RE (95% CI) = 1.19 (0.53, 1.85), P=0.0004].

There was substantial heterogeneity (I^2 = 99%, P<0.00001) in the reported pooled data for FAI across the 6 researchers who reported on both the intervention and comparison groups. The data was combined using a random-effects model. Figure 2 shows that there was no significant difference or connection in FAI between the intervention and control groups [RE (95% CI) = 0.96 (-2.06, 3.98), P=0.53].

There was substantial heterogeneity (I^2 = 68%, P=0.001) in the pooled results for HOMA-IR between the intervention and comparison groups, which were reported by 10 researchers. To aggregate the data, a random-effects model was applied. Figure 2 displays that there was no statistically significant difference or association between the intervention and control groups with respect to HOMA-IR [RE (95% CI) = -0.36 (-0.69, -0.02), P=0.04].

There was no significant heterogeneity between the 9 studies (I^2= 0%, P=0.70) that provided pooled results for Total T in the intervention and comparison groups. To aggregate the data, a random-effects model was applied. Total T was significantly different between the intervention and comparison groups (Figure 2, RE (95% CI) = -0.12 (-0.18, -0.05), P=0.0008).

All intervention and control group comparison metrics showed statistically significant heterogeneity (I^2 = 99%, P<0.000001). All of the data werecombined using a random-effects model. As can be seen in Figure 2, there was a significant difference and association between the intervention group and the comparison group [RE (95% CI) = 0.34 (0.02, 0.67), P=0.0005].

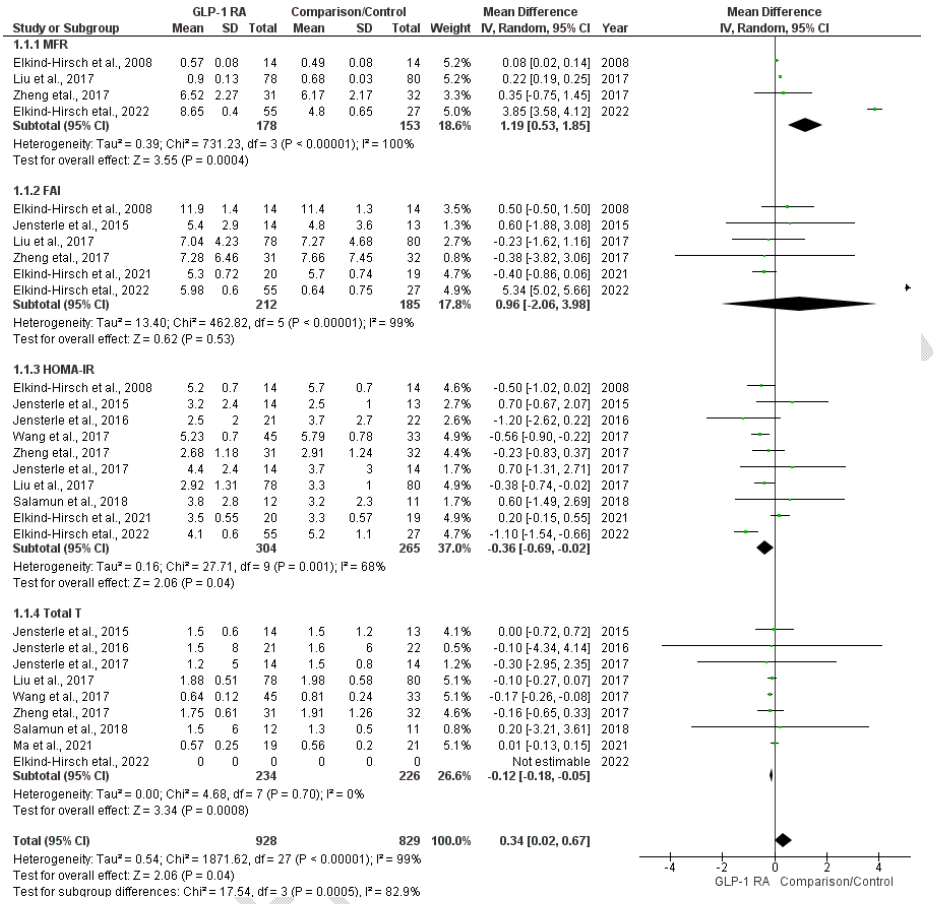

Figure 2. Forest plot for comparison of intervention and comparison / control group (Menestral frequency rate (MFR), Free Androgen Index (FAI), Homeostasis Model Assessment-estimated Insulin Resistance (HOMA-IR), and Total Testosterone (Total T).

Quality assessment

There was a low risk of bias in 7 studies and some concerns in 7 studies, while no high risk of bias was found in any investigation in the domain of randomization bias. A low risk of bias was found in the remaining domains. Overall, there was a low risk of bias in 7

studies. Seven studies had some concerns, while no study had a high risk of bias (Figure

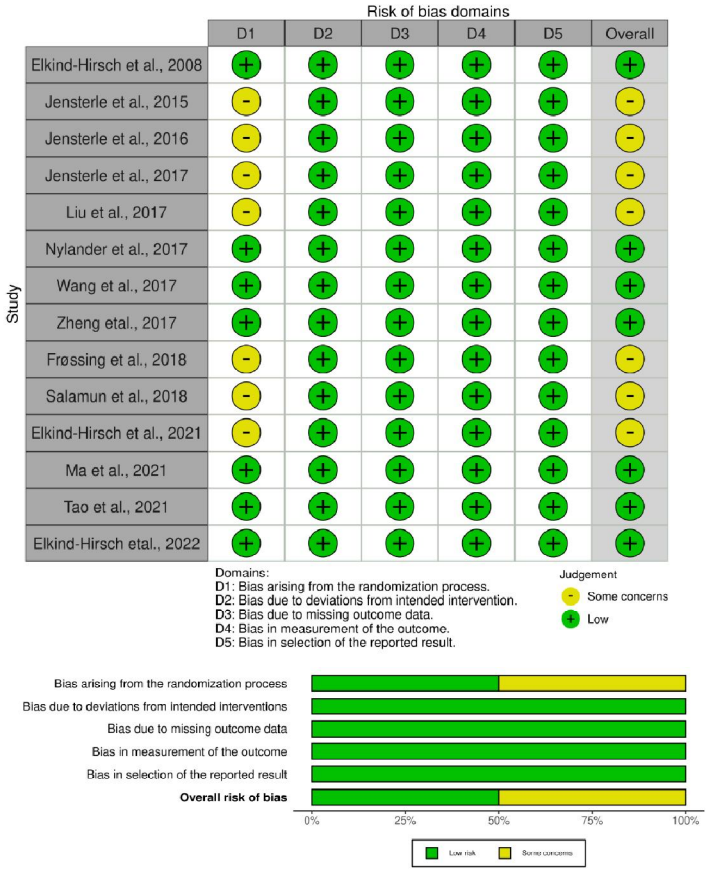

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Figure 3. Risk of bias in the included studies.

Discussion

Polycystic ovarian syndrome (PCOS) is a multifactorial illness with strong epigenetic and environmental influences [37, 38]. It affects a variety of bodily systems and molecular

pathways. Obesity is strongly linked to PCOS, and particularly abdominal obesity, despite the fact that many people with PCOS have more subcutaneous fat than controls. In order to enhance the clinical care of overweight and obese women with PCOS [39, 40], it is essential to develop multi-targeted therapy strategies that simultaneously address both modifiable weight-dependent and independent variables. Meanwhile, multiple new therapeutic drugs for controlling type 2 diabetes have recently been developed, increasing the range of possible PCOS treatments. GLP-1RAs are being looked at more closely as a possible therapeutic approach for PCOS control [41]. Thus, the present systematic review and meta-analysis were designed to present the available literature to assess the efficacy of GLP-1 RAs in women with PCOS.

In the present study, when GLP-1 RA drugs were used alone and compared with placebo or other single drug such as Metformin, GLP-1 RA gave better results in terms of reducing BMI, and improving inulin sensitivity. Which are in line with the findings of another systematic review, and researchers concluded that insulin sensitivity was improved by GLP-1 RAs (SMD -0.40, 95% CI -0.74 to -0.06, P = 0.02), and both BMI and abdominal girth were decreased (SMD -1.02, 95% CI -1.85 to -0.19, P = 0.02) and (SMD -0.45, 95% CI -0.89 to -0.00, P = 0.05) respectively when compared with Metformin[42]. Another study also supports the present study's findings as they concluded that, in terms of weight loss, reduction in WC, and BMI, a meta-analysis found that the

antiobesity efficacy of GLP-1RAs was superior to Metformin [43].The question can arise why GLP-1 RA is better than other drugs, especially Metformin which is the choice drug of most physicians the possible explanation can be that GLP-1 RA increased insulin sensitivity in adipose, muscle, and liver tissues which was shown to be the direct result of a GLP-1 RA by Lee, Park [44]. In addition, a GLP-1 RA also improves insulin resistance via a series of indirect mechanisms as well as alterations in energy utilization efficiency, suppression of fat synthesis and stimulation of lipolysis in the liver, and inhibition of a fructose-induce [45]. However, a GLP-1 RAand Metformin both improved insulin sensitivity and insulin resistance in patients with PCOS, but the GLP-1 RAs showed better efficacy, as shown by the results of the current study.Similarly, studies have shown that GLP-1 RAismore effective than lifestyle modifications or metformin in helping people lose weight, and that they also have additional metabolic, reproductive, and CVD benefits for the PCOS group of people[46]. The present study also concluded that when GLA-1 RA is combined with Metformin or any other drug, its efficacy increases. These findings align with the results of a study that combined therapy was superior to GLP-1 RA and Metformin monotherapy in lowering weight, BMI, and WC. The combinedtherapy-treated group dropped an average of 6.5±2.8 kg, while the GLP-1 RA group lost an average of 3.8±3.7 kg, and the Metformin group lost an average of 1.2±1.4 kg ($P<0.001$)[47]. Meanwhile, GLP-1 RAs are not yet universally accepted by the medical community. Since using GLP-1

RAs necessitates both effective contraception during therapy and a washout time before to conception, balancing reproductive and metabolic treatment techniques is of primary concern[46]. However, when administered alone or in conjunction with metformin, both GLP-1 RA (Exenatide and Liraglutide) are effective treatments for PCOS. Women with PCOS who are overweight or obese, glucose intolerant, have CVD or its risk factors or are trying to conceive should give GLP-1 RAs serious thought while designing a treatment plan[14]. In addition, according to the present meta-analysis, GLP-1 RA alone or in combination was compared with Metformin/comparison/placebo in terms of MFR, FAI, HOMA-IR and Total T. It was concluded that GLP-1 RA had a significant effect in terms of MFR and Total T which concluded that intervention of GLP-1 RA has much better effect than comparison group while there was non-significant or equal effect interms of FAI and HOMA-IR its mean both GLP-1 RA and conparison has positive effects.

The incidence of adverse events was compared between GLP-1RAs alone or in combination, and drugs in comparison, such as Metformin alone or in combination in our study and nausea and headache was found to be the most prevalent adverse events occurred. Nonetheless, a review by Lamos found that GLP-1RAs were generally well-tolerated, with the most serious adverse effect being nausea[3]. In spite of this, research has revealed that GLP-1 RA-induced nausea typically subsides over time, and may be linked to variations in the maximum plasma concentrations of the drug [48]. Additionally,

a meta-analysis conducted by Han, patients with PCOS who were given GLP-RAs were more likely to havea headache than those who were given Metformin, whereas there was no difference in the occurrence of any other side effects[42].Headache is an uncommon side effect that is linked to regular dosing. A GLP-1 receptor agonist was associated with a greater rate of nausea and headaches than metformin. Importantly, a low dose ofLiraglutide (1.2 mg once a day) was utilized in all studies reporting this incident [30, 47].Infact, the efficacy and safety of GLP-1 RAs, in overweight and obese women with PCOS, and to explain the benefit/risk profile of its administration necessitate larger, longer, well-organized, multi-centre, double-blind, placebo-controlled trials, with rigorous designs and greater follow-up. There needs to be a unified approach to addressing the major consequences of hormones, metabolism, and reproduction. Insight into the potential involvement of GLP-1 RAs will allow clinicians to personalize future targeted therapy methods based on the patient's phenotype and needs, ultimately leading to better long-term therapeutic outcomes.

Strengths and Limitations

There are strengths and limitations of the current study. Even though there are meta-analyses performed in this field, but they were limited to Metformin. Still, in the present meta-analysis, we focused on Metformin and its combination with other drugs and GLP-1 RAs. According to our knowledge, there was no meta-analysis which compared variables

such as MFR, HOMA-IR, FAI and Total T in a single study. Most of the studies were performed to see the effects on BMI and CW. Treatment with the medication Metformin is recommended for women with PCOS. The current study compared the efficacy and safety of a GLP-1 RA for PCOS to that of Metformin and GLP-1 RA, both of which have been shown to be effective.

Even though this study highlighted the importance of the GLP-1 RAs but still current study had some limitations which should be addressed. Firstly, there are a limited number of research articles which may be due to strict inclusion criteria as only RCTs were included in the present review. Secondly, studies included were with limited sample size, which is also highlighted in the current review. Thirdly, the sample size was too small to use a funnel plot to determine whether or not there was a publication bias in the papers that were included. Fourth, studies included in the present review were from countries such as China, the USA, and Europe, which had a diverse populations that can affect efficacy, and adverse events can occur due to the immune system, which may differ. Fifth, the difference in the follow-up period may affect the findings as some studies followed for 12 weeks, and some 24 and 32 weeks.

Conclusions

Regarding women of reproductive age, PCOS is the most prevalent ovarian condition. Depending on the population studied and the diagnostic criteria used, the incidence of

PCOS ranges from 6.1% to 19.9%. Different treatments, such as Metformin and GLP-1 RAs, were used. Thus, the present systematic review and meta-analysis were designed to assess the efficacy and safety of GLP-1 RAs used in women with PCOS. In the present study, GLP-1 RA medications alone produced superior outcomes in lowering BMI and increasing insulin sensitivity than the placebo or any other single medicine tested, including Metformin. It was also determined that GLA-1 RA's efficacy is enhanced when coupled with Metformin or other medication. The meta-analysis examined GLP-1 RA alone or in combination with Metformin / comparison / placebo in terms of MFR, FAI, HOMA-IR, and Total T. The MFR and Total T results showed that GLP-1 RA was significantly more effective than the control group. Still, the results were inconclusive or equal for FAI and HOMA-IR, indicating that both GLP-1 RA and the control group were beneficial. Our study revealed that nausea and headache were the most common adverse events when comparing GLP-1RAs alone or in combination with medicines like Metformin alone or in combination. Seven studies presented a low risk of bias, while seven others did. GLP-1 RAs can be the best option for the treatment of PCOS. However, future research with high-quality research articles is needed.

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Comment [HC6]: Reference no 5, 28 is incomplete. or not as per Vancouver style. Rewrite these references as per Vancouver style.