Available online at
https://ijpncs.uitm.edu.my/index.php/en/

IJPNaCS International Journal of Pharmaceuticals, Nutraceuticals and Cosmetic Science
e-ISSN: 2682-8146

International Journal of Pharmaceuticals, Nutraceuticals and Cosmetic Science
9(1) 2026, 159-173

International Journal of Pharmaceuticals, Nutraceuticals and Cosmetic Science

Efficacy and safety of metformin and liraglutide combination therapy in comparison with metformin in managing metabolic and endocrine levels of PCOS: A systematic review

Carl Jefferson E. Bernales[1], Frances Alyza A. Oclos[1], Jhedka C. Suñga[1], Ronna Nicole M. Tagalog[1*], Leanne Christine S. Tantiado[1], Jebb Patrick M. Delos Santos[1], Mac Ardy Gloria[2]

[1]*School of Pharmacy, Far Eastern University – Dr. Nicanor Reyes Medical Foundation, Regalado Ave., West Fairview Quezon City, 1118, Philippines*
[2]*College of Pharmacy, University of the Philippines Manila, 670 Padre Faura St, Ermita, Manila, 1000 Metro Manila, Philippines*

ARTICLE INFO

Article history:
Received 28 February 2026
Revised 01 May 2026
Accepted 11 June 2026
Online first
Published 29 June 2026

Keywords:
Polycystic ovarian syndrome,
Metformin,
Liraglutide,
Metabolic,
Endocrine

DOI:
10.24191/IJPNaCS.v9i1.10

ABSTRACT

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder causing various metabolic and endocrine dysfunctions. Research shows that women with PCOS who experience severe symptoms often report a diminished quality of life, largely due to concerns about physical appearance, reproductive challenges, and metabolic health issues. PCOS impacts daily life, highlighting the complex interplay between medical, emotional, and social aspects of the condition. Effective PCOS management improves patients' health and quality of life. This review compares the efficacy and safety of metformin plus liraglutide versus metformin monotherapy in managing metabolic and endocrine levels in women with PCOS. Articles were systematically retrieved from PubMed, Elsevier, and Scopus databases, complemented by manual searches from inception to 2024. Data were extracted using structured forms, analyzed qualitatively, and evaluated for bias using the Cochrane Risk of Bias Tool 2. The review includes RCTs on women with PCOS, aged 18 years and older, with a BMI of at least 24kg/m². Studies were excluded if they were not original, relied on secondary data, involved animal testing, lacked sufficient information, were non-translatable, contained unextractable data, were duplicates, or assessed metformin against interventions other than liraglutide. Combination therapy demonstrated advantages over monotherapy, where participants showed notable reductions in BMI, waist circumference, and insulin resistance (HOMA-IR). Improvements in lipid profiles were observed, including reductions in LDL and triglyceride levels alongside increases in HDL levels. This systematic review highlights the superior efficacy and manageable safety profile of metformin-liraglutide therapy in managing metabolic and endocrine dysfunctions in women with PCOS. Improvements in key parameters suggest combination therapy as an effective option. While side effects were reported, they were mild to moderate and did not detract from overall advantages. Future research with larger sample sizes and longer durations is warranted to confirm findings and investigate long-term benefits.

[1*]Corresponding author. *E-mail address*: ronna.tagalog@astra.feu-nrmf.edu.ph

1. INTRODUCTION

Polycystic ovary syndrome (PCOS), which affects approximately 4%–20% of reproductive-aged women globally, remains a significant but under-recognized health issue. Deswal et al. (2020) stated that PCOS is a hormonal disorder that disrupts ovarian function, leading to excessive androgen production and hormonal imbalances. The American Society for Reproductive Medicine (ASRM) has recognized the broad metabolic impact of PCOS and endorsed renaming it to polyendocrine metabolic ovarian syndrome (PMOS). This shift reframes PCOS from being seen merely as a complex, long-term hormonal disorder to a condition with clearer metabolic focus, allowing for more appropriate and effective treatment approaches. Women with PCOS often face multiple comorbidities, including obesity and poor glucose metabolism, which increase the risk of diabetes, dyslipidemia, hypertension, and metabolic syndrome—all of which significantly contribute to systemic morbidity and diminish health-related quality of life.

Metformin, an insulin-sensitizing drug primarily used to treat type 2 diabetes, has become the leading medication for managing insulin resistance in PCOS due to its effectiveness in lowering blood sugar levels without causing weight gain or hypoglycemia (Kumar et al., 2016). It also offers additional benefits, such as reducing cholesterol levels, lowering the risk of heart disease, promoting regular menstrual cycles and ovulation, and reducing miscarriage risk. Liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist used for diabetes management and weight loss, enhances insulin secretion and promotes significant weight loss (Nylander et al., 2017).

Given that weight reduction is the primary modifiable risk factor for PCOS, treatment strategies have been developed for overweight or obese women with this condition. Despite the use of medications and lifestyle modifications, many individuals with PCOS continue to exhibit obesity that is refractory to conventional interventions, highlighting the potential of liraglutide as a promising alternative treatment. Comparative research evaluating the efficacy and safety of metformin monotherapy versus a liraglutide plus metformin combination therapy in managing PCOS and associated metabolic disturbances is needed to determine which medication regimen offers superior benefits for weight management and endocrine levels, thereby enhancing overall treatment efficacy in this patient population.

2. MATERIAL & METHODOLOGY

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PRISMA Executive, 2014). The study protocol was registered with PROSPERO prior to execution (Registration No. CRD42024603187).

2.1 Design of study

An electronic literature search from database inception through 2024 was conducted using PubMed, Scopus, and ClinicalTrials.gov. The search was restricted to articles published in English or those with available translations. The search strategy employed the terms “Polycystic Ovarian Syndrome,” “Metformin,” and “Liraglutide,” combined with Boolean operators (AND/OR). The detailed search strings and associated databases are presented in Table 1.

https://doi.org/10.24191/IJPNaCS.v9i1.10

Table 1. Search strings and where they were used.

Database	Search String
PubMed	(PCOS or polycystic ovarian syndrome) OR (hirsutism) OR (hyperandrogenism) AND (GLP-1 receptor agonist) OR (glucagon-like peptide 1 receptor agonist) OR (liraglutide) AND (metformin) Filters: Clinical Trial, Randomized Controlled Trial
Scopus	(TITLE-ABS-KEY (ovar* AND disease) OR TITLE-ABS-KEY (pcos) AND TITLE-ABS-KEY (liraglutide) AND TITLE-ABS-KEY (metformin))
Clinical Trial Registries such as: ● ClinicalTrials.gov	- Condition/disease ● PCOS - Other terms ● Polycystic Ovary Syndrome - Intervention/treatment ● Liraglutide or metformin

2.2 Study selection

The selection of studies was performed by two reviewers who evaluated articles through abstract and full-text screening. Articles that failed to meet the inclusion criteria were excluded and systematically coded in accordance with a comprehensive manual to maintain uniformity. Exclusion criteria encompassed studies that did not involve clinically diagnosed women with PCOS, studies comparing metformin with therapies other than liraglutide, or studies that failed to evaluate metabolic and endocrine outcomes. Additional exclusion categories encompassed non-randomized trials, non-original papers, inadequate data, duplicates, translation issues, and animal studies. Each rejected study was assigned a distinct code (1–10) to clearly elucidate the rationale. All included and excluded studies were documented, and any discrepancies between the two reviewers were reconciled through discussion, thereby ensuring transparency and reliability in the selection process.

2.3 Data extraction

Publication information: Title, author, year of publication, journal name, country, conflict of interest, and funding sources.

1. Study design: Context, design, time frame, and sampling method.
2. Participants: Age, sex ratio, race/ethnicity, sample size, inclusion/exclusion criteria, withdrawals/exclusions.
3. Methodological characteristics: Start and end dates, participant screening tool, randomization process, study delimitations, ethical sanction.
4. Intervention characteristics: Number of participants, theoretical basis, description, duration, administration schedule, delivery, and provider assigned.
5. Comparator characteristics: Number of participants, theoretical basis, concise description, duration, and assigned provider.
6. Measures of outcomes: Timepoints measured, person responsible, unit of measurement, scales used, instrument validation, imputation of missing data, risk estimate, power, and response rate.
7. Data for pooling, if available (sample size, mean, standard deviation, and the p-value).

https://doi.org/10.24191/IJPNaCS.v9i1.10

2.4 Quality assessment and risk of bias

The quality of the included studies was assessed using the Cochrane Risk of Bias tool (RoB 2; Cochrane, 2019), concentrating on domains including randomization, outcome measurement, and reporting bias. Two independent reviewers assessed each study, and any discrepancies were reconciled through consensus or, if necessary, consultation with a third reviewer.

2.5 Data processing and qualitative analysis

The characteristics of the included studies were analyzed through frequency statistics, and a narrative synthesis was conducted using the extracted data. Studies were evaluated across five primary domains of interest:

1. Participant characteristics (i.e., women diagnosed with PCOS)**;**
2. Methodological characteristics (i.e., randomized controlled trials)**;**
3. Characteristics of the Intervention and Comparator Groups (LIRA/MET)**;**
4. Characteristics of the Outcome Measured (Metabolic and Endocrine outcomes); and
5. Risk of bias (RoB 2)

3. RESULTS

3.1 Search results

Following the execution of the search strategies across the three databases, the initial search retrieved a total of 1,838 studies. All 1,838 studies were screened against the eligibility criteria, resulting in the exclusion of 1,835 articles based on the ineligibility coding. After this screening, three articles met the inclusion criteria and were subjected to qualitative analysis. The completed PRISMA flow diagram in Fig. 1 summarizes this entire process. Metabolic and endocrine outcomes were qualitatively analyzed and are presented in the tables, comparing metformin monotherapy with a liraglutide–metformin combination therapy.

The reviewed studies exhibited notable strengths, although their reliability was impacted by a high risk of bias, which is illustrated in the risk of bias summary (Fig. 2). Specifically, the open-label design of these trials introduced potential detection bias in outcome measurement. Despite this limitation, **a** detailed analysis was conducted to evaluate how metformin monotherapy, as well as its combination with liraglutide, affected various metabolic and endocrine functions.

https://doi.org/10.24191/IJPNaCS.v9i1.10

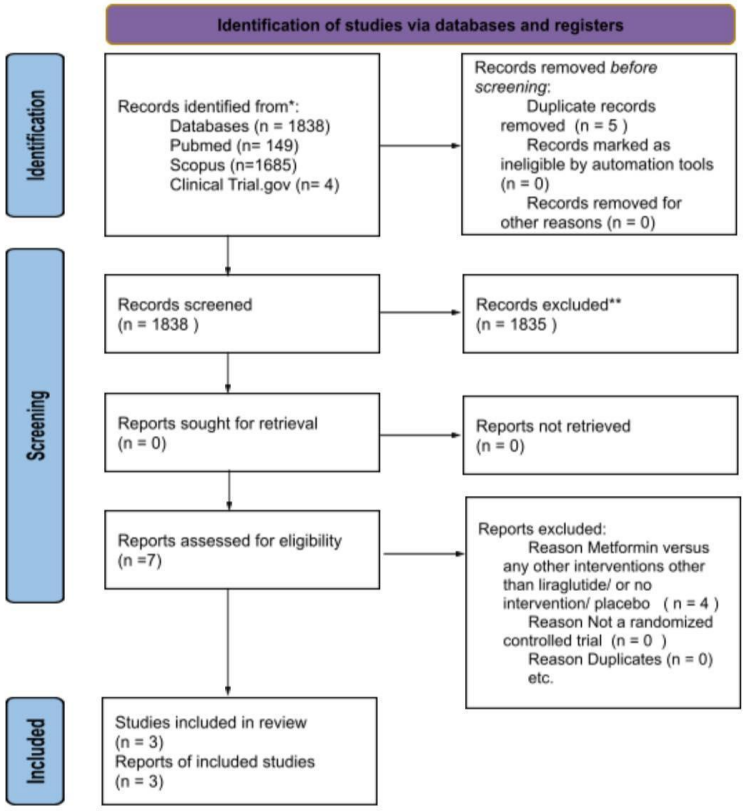

Fig. 1. Accomplished PRISMA flowchart.

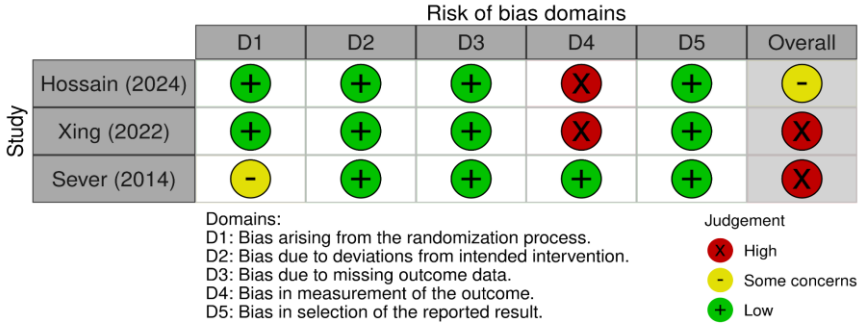

Fig 2**.** Risk of Bias Summary

https://doi.org/10.24191/IJPNaCS.v9i1.10

3.2 Characteristics of included studies

The characteristics of the selected articles are outlined in Table 2. The studies involved a total of 101 randomly assigned patients across the treatment and comparator groups. The studies employed different methods for sequence generation in their randomization processes. Hossain et al. (2023) utilized a computer-generated random number chart via the RAND function in Excel, whereas Sever et al. (2014) adopted simple randomization techniques to ensure unbiased participant allocation. All three articles (Hossain et al., 2023; Jensterle Sever et al., 2014; Xing et al., 2022) followed an open-label RCT design, with Jensterle Sever et al. (2014) and Xing et al. (2022) also incorporating a prospective approach. Two studies compared metformin monotherapy versus a combination therapy of liraglutide and metformin, while one study compared the combination treatment of metformin and liraglutide versus liraglutide or metformin alone. The included studies followed the Rotterdam criteria for PCOS diagnosis (Christ & Cedars, 2023). The target populations consisted of women with PCOS ranging in age from 15 to 45 years who were monitored over follow-up periods ranging from 4 to 12 weeks.

Table 2. Interventor, comparator, and PCOS diagnosis criteria in the studies.

Author, Yr	Interventor	Comparator	Duration (weeks)	PCOS Diagnosis Criteria	Age Group	BMI (kg/m²)	Ethics Review	Funding
Hossain et al., (2024)	Short-term and low-dose liraglutide (subcutaneous injection of 1.2 mg once daily) plus metformin (500 mg orally twice daily)	Metformin Group (500 mg twice daily orally)	12	Rotterdam criteria	15 and 45 years old	≥27.5	Approved by Specific Ethics Committee	This research received partial funding through a grant from the Research and Development department of BSMMU, with additional support from Novo Nordisk Pharma and Beximco Pharmaceuticals Ltd. in Bangladesh.
Sever et al., (2014)	Combined MET 1000 mg BID, and LIRAGLUTIDE 1.2 mg QD s.c. (COMBI)	Metformin Group: metformin (MET) 1000 mg BID, or Liraglutide (LIRA) 1.2 mg QD s.c.,	12	Rotterdam Criteria	18 and 40 years old	≥ 24	Approved by Specific Ethics Committee	This research was made possible through funding from the Science and Technology Department's People's Livelihood Science and Technology Joint Program in Liaoning Province
Xing et al., (2022)	Combination of liraglutide and vs. metformin alone LIRAGLUTIDE 1.2 mg QD s.c. plus MET 1000 mg BID p.o.	Metformin Group: MET 1000 mg BID p.o.	12	Rotterdam Criteria	18 and 40 years old	≥ 24	Approved by Specific Ethics Committee	This study was supported through funding from the Science and Technology Department's People's Livelihood Science and Technology Joint Program in Liaoning Province.

3.3 Anthropometric outcomes

In Table 3, according to Hossain et al. (2023), combination therapy with liraglutide and metformin (MET/LIRA) reduces BMI more than metformin monotherapy. This improves the overall effectiveness of the intervention. As for Xing et al. (2022), combining liraglutide and metformin resulted in a 2.4 ± 1.0 decrease compared to 1.3 ± 1.3 for liraglutide and 0.5 ± 0.5 for metformin alone. Waist circumference data was only accessible to Sever et al. (2014). Combined therapy with liraglutide and metformin significantly decreases waist circumference by 5.5 ± 3.8 cm compared to monotherapy with LIRA (3.2 ± 2.9 cm) and MET (1.6 ± 2.9 cm). In the research of Sever et al. (2014), the combination of metformin and liraglutide resulted in the greatest waist reduction.

Table 3. A summary of clinical studies with anthropometric outcomes.

Author, Yr	Intervention	Anthropometric Measurement (*mean* ± *SD*)			
		a. BMI (kg/㎡)		b. Waist Circumference (cm)	
		Before	After	Before	After
Hossain et al., (2024)	MET	32.8±3.3	32.2 ± 3.7		
	MET/LIRA	34.7 ± 3.7	33.0 ± 3.7		
Sever et al., (2014)	MET	36.6 ± 3.5	36.1 ± 3.8	122.3 ± 7.0	120.7 ± 7.8
	LIRA	39.3 ± 4.2	37.9 ± 4.0	124.9 ± 9.9	121.7 ± 9.6
	MET/LIRA	37.6 ± 5.1	35.3 ± 5.5	121.9 ± 17.7	116.4 ± 18.4
Xing et al., (2022)	MET	28.80 ± 4.25	26.88 ± 3.76		
	MET/LIRA	29.69 ± 3.44	26.24 ± 2.75		

3.4 Metabolic outcomes

Tables 4 and 5 summarize the different metabolic effects observed across the included studies when assessing the glucagon-like peptide-1 receptor agonist (GLP-1 RA) MET/LIRA against MET monotherapy in women with PCOS. Two of the studies found that the homeostatic model assessment for insulin resistance (HOMA-IR) score improved, suggesting reduced insulin resistance, whereas Sever et al. (2014) observed no significant change in either group. Specifically, Hossain et al. (2023) reported that compared to MET alone, the combination of MET/LIRA significantly decreased insulin resistance (p = .026). Similarly, Xing et al. (2022) found that the combination treatment reduced insulin resistance more effectively than monotherapy; the MET/LIRA group demonstrated a significant improvement, with baseline HOMA-IR scores decreasing from 4.85 ± 2.09 to 2.62 ± 1.05 after 12 weeks. Regarding glycemic and lipid regulation, Sever et al. (2014) noted that 42% of individuals with impaired glucose tolerance improved following the intervention, although outcomes were mixed across the treatment cohorts. Additionally, metabolic syndrome resolved in three liraglutide-treated patients, whereas participants in several other groups continued to exhibit the condition. Following a 120-minute oral glucose tolerance test

(OGTT), the combination therapy dramatically reduced glucose levels (p = .006 vs. metformin monotherapy). The lipid profile analysis indicated that while liraglutide enhanced insulin sensitivity and lowered LDL and triglyceride levels, metformin lowered HOMA-IR values and slightly increased HDL levels. However, Sever et al. (2014) also observed that while the combination treatment lowered LDL and insulin output, it gradually increased HOMA-IR over time in their specific cohort, implying a potential risk of rebound insulin resistance. Ultimately, these three studies demonstrate that both combination therapy and monotherapy can significantly alter metabolic markers in women diagnosed with PCOS, as summarized in Table 4.

Table 4. A summary of metabolic outcomes associated with glycemic profile changes in clinical studies

Author, Yr	**Intervention**	**Glycemic Profile**			
		HOMA-IR (*mean, range, standard deviation, median, and interquartile range*)		**Insulin** (*mean, range, standard deviation,median, and interquartile range*)	
		Before	After	Before	After
Hossain. et al., (2024)	MET	3.7 (2.5 - 5.0)	3.9 (2.4 - 5.2)	17.4 (11.7 - 26.4) µIU/mL	16.6 (11.7 - 28.5) µIU/mL
	MET/LIRA	4.9 (3.8 - 6.9)	3.3 (2.3 - 5.2)	20.8 (18.5 - 25.9) µIU/mL	15.4 (10.9 - 22.2) µIU/mL
Sever. et al., (2014)	MET	3.8 (3.8)*	2.5 (2.4)*	12.3 (13.3)* mU/l	12.7 (8.3)* mU/l
	LIRA	2.4 (2.3)*	2.1 (2.0)*	59.2 (97.0)* mU/l	68.4 (88.1)* mU/l
	MET/LIRA	1.7 (4.9)*	2.1 (2.9)*	7.7±1.8 mU/l	5.8±1.3 mU/l
Xing. et al., (2022)	MET	4.53 ± 3.07	2.86 ± 2.05		
	MET/LIRA	4.85 ± 2.09	2.62 ± 1.05		

*indicate the difference between median - interquartile range

3.5 Endocrine outcomes

Hossain et al. (2023) and Sever et al. (2014) demonstrated that MET and MET/LIRA improved gonadal function, as detailed in Table 6. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), and Total testosterone (TT) levels increased dramatically after 12 weeks with the combination drug, improving menstruation control and ovarian follicle production. MET/LIRA decreased TT better than metformin. No substantial difference was seen in FSH, or LH/FSH ratio.

In three clinical trials, MET/LIRA therapies resulted in a greater reduction in TT levels than metformin monotherapy while no other hormone parameters were altered. Higher rates of adverse events were reported with the combination therapy group in study by Hossain et al. (2023), indicating a potential trade-off between efficacy and tolerability.

https://doi.org/10.24191/IJPNaCS.v9i1.10

In clinical studies, MET/LIRA lowers hormone levels in PCOS women. Hossain et al. (2023) and Xing et al. (2022) reported notable drops in TT across their respective trials, with values decreasing from 2.1 to 1.6 nmol/L, 52.2 to 44.8 ng/dL, and 0.79 to 0.62 ng/mL. Furthermore, Sever et al. (2014) observed that LH levels increased from 6.4 to 8.5 mIU/mL, while Xing et al. (2022) reported a decrease from 12.09 to 6.61 mIU/mL. The latter study also demonstrated a reduction in FSH from 6.22 to 4.42 mIU/mL. These hormonal improvements demonstrate that combination therapy regulates the hypothalamic–pituitary–ovarian axis more effectively than monotherapy (Xing et al., 2022).

3.6 Side effects of monotherapy (MET) and combination therapy (MET/LIRA)

Combination therapy with liraglutide and metformin has been shown to effectively enhance glycemic control, offering significant benefits for managing diabetes and related metabolic conditions (Hossain et al., 2023; Jensterle et al., 2022; Xing et al., 2022). Although this regimen is associated with mild-to-moderate adverse events—such as gastrointestinal distress (nausea, vomiting, diarrhea, and heartburn), insomnia, and occasional hypoglycemia—these reactions are generally manageable and typically resolve within the first two weeks of treatment (Hossain et al., 2023; Sever et al., 2014). Temporary rashes at the injection site were also reported (Hossain et al., 2023). Overall, the therapeutic benefits of the combination therapy outweigh these mild and transient side effects, making it a valuable treatment option for women with PCOS (Jensterle et al., 2022; Xie et al., 2023).

https://doi.org/10.24191/IJPNaCS.v9i1.10

Table 5. A summary of metabolic outcomes associated with lipid profile changes in clinical studies.

Author, Yr	Intervention	Lipid Profile					
		High-Density Lipoprotein *(mean, range, standard deviation)*		**Low-Density Lipoprotein** (*mean, standard deviation*)		**Triglycerides** (*mean, range, standard deviation*)	
		Before	After	Before	After	Before	After
Hossain. et al., (2024)	MET	40.5 (35.8 - 48.8) mg/dL	45 (39.8 - 51.0) mg/dL	134.7 ± 41.4 mg/dL	123.5 ± 30.4 mg/dL	122.0 (92.0 - 193.3) mg/dL	122.5 (101.8 - 162.5) mg/dL
	MET/LIRA	40.5 (36.5 - 42) mg/dL	42 (39.8 - 47.3) mg/dL	125. 1 ± 24.6 mg/dL	123.4 ± 27.5 mg/dL	149 (130.8 - 166.5) mg/dL	131.5 (113-172) mg/dL
Sever. et al., (2014)	MET	1.1±0.2 mmol/L OR 42.5 ± 7.7 mg/dL	1.2±0.2 mmol/L OR 46.4 ± 7.7 mg/dL	2.9±0.6 mmol/L OR 112.1 ± 23.2 mg/dL	2.9±0.5 mmol/L OR 112.1 ± 19.3 mg/dL	1.6 (0.5)* mmol/L OR 61.9 ± 19.3 mg/dL	1.3 (0.5)* mmol/L OR 50.3 ± 19.3 mg/dL
	LIRA	1.1±0.3 mmol/L OR 42.5 ± 11.6 mg/dL	1.1±0.2 mmol/L OR 42.5 ± 7.7 mg/dL	3.2±0.8 mmol/L OR 123.7 ± 30.9 mg/dL	3.1±0.5 mmol/L OR 119.9 ± 19.3 mg/dL	1.4 (1.1)* mmol/L OR 54.1 ± 42.5 mg/dL	1.1 (1.4)* mmol/L OR 42.5 ± 54.1 mg/dL
	MET/LIRA	1.3±0.4 mmol/L OR 50.3 ± 15.5 mg/dL	1.1±0.4 mmol/L OR 42.5 ± 15.5 mg/dL	3.4±0.8 mmol/L OR 131.5 ± 30.9 mg/dL	2.9±0.8 mmol/L OR 112.1 ± 30.9 mg/dL	1.4 (0.4)* mmol/L OR 54.1 ± 15.5 mg/dL	1.4 (0.5)* mmol/L OR 54.1 ± 19.3 mg/dL

Table 6. A summary of clinical studies with endocrine outcome.

Author, Yr	Intervention	Sex Hormones					
		TT (*mean, standard deviation*)		**LH** (*mean, range, and standard deviation*)		**FSH** (*mean, range, and standard deviation)*	
		Before	After	Before	After	Before	After
Hossain. et al (2024)	MET	46.1 ± 15.1 ng/dL	48 (37.7-83.3) ng/dL	7.3 (3.6-9.6) IU/mL OR 7300 mIU/mL	8.5 (5.2-16.5) IU/mL OR 8500 mIU/mL	3.9±1.6 IU/mL OR 3900 mIU/mL	4 (3.5-5.4) IU/mL OR 4000 mIU/mL
	MET/LIRA	52.2 ± 24.8 ng/dL	44.8(37.3-83.3) ng/dL	6.4 (4.8-9.6) IU/mL OR 6400 mIU/mL	8.5 (5.2-16.5) IU/mL OR 8500 mIU/mL	5.7 ± 1.5 IU/mL OR 5700 mIU/mL	4.0 (3.5 - 5.4) IU/mL OR 4000 mIU/mL
Sever. et al., (2014)	MET	1.7±1 nmol/l OR 49.0 ng/dL	1.5±0.9 nmol/l OR 43.3 ng/dL				
	LIRA	1.8±1.1 nmol/l OR 51.9 ± 31.7 ng/dL	2.2±1.4 nmol/l OR 63.4 ± 40.4 ng/dL				
	MET/LIRA	2.1±1.3 nmol/l OR 60.6 ± 37.5 ng/dL	1.6±0.7 nmol/l OR 46.1 ± 20.2 ng/dL				
Xing. et al., (2022)	MET	0.84 ± 0.25 ng/mL OR 84 ± 25 ng/dL	0.79 ± 0.31ng/mL OR 79 ± 31 ng/dL	11.97 ± 4.20 mIU/mL	9.77 ± 5.81mIU/mL	6.03 ± 1.48 mIU/mL	5.28 ± 2.11 mIU/mL
	MET/LIRA	0.79 ± 0.20 ng/mL 79 ± 20 ng/dL	0.62 ± 0.24 ng/mL 62 ± 24 ng/dL	12.09 ± 5.26 mIU/mL	6.61 ± 4. 72 mIU/mL	6.22 ± 1.44 mIU/mL	4.42 ± 2.59 mIU/mL

TT- Testosterone; LH- Luteinizing Hormones; FSH- Follicle-Stimulating Hormones

4. DISCUSSION

PCOS is a complex endocrine and metabolic disorder diagnosed using the Rotterdam criteria, which require at least two of the following: chronic anovulation, hyperandrogenism, or polycystic ovarian morphology (Shukla et al., 2025). Management primarily begins with lifestyle modifications, including a proper diet and regular physical activity, especially for weight control. However, pharmacologic therapy is often necessary to address insulin resistance and hormonal imbalances.

Metformin has long been used as a first-line treatment for PCOS due to its ability to improve insulin sensitivity, regulate menstrual cycles, and enhance metabolic parameters, even in non-obese women. The populations included in the reviewed randomized controlled trials—which compared metformin monotherapy with a combination therapy of metformin and liraglutide—primarily consisted of overweight and obese women (defined as a BMI ≥ 24 or ≥ 27.5 kg/m^2), rather than non-obese individuals. The findings of these trials demonstrated that combination therapy led to greater improvements in weight reduction, fasting insulin levels, lipid profiles, and hormonal balance compared to monotherapy (Hossain et al., 2023; Jensterle Sever et al., 2014; Xing et al., 2022).

These results suggest that targeting multiple metabolic pathways simultaneously may provide enhanced benefits; however, future research is needed to determine whether these advantages extend to non-obese PCOS patients, who are often overlooked in metabolic research. The combined approach appears promising in managing both endocrine and metabolic complications, potentially advancing individualized treatment strategies (Xie et al., 2023). However, the interpretation of these findings must consider limitations such as small sample sizes, short treatment durations, and potential study design biases, which may affect their generalizability. Additionally, both medications were associated with gastrointestinal adverse effects, including nausea, vertigo, and diarrhea, which may influence patient adherence (Hossain et al., 2023; Jensterle Sever et al., 2014; Xing et al., 2022). Overall, the evidence supports the potential advantage of combination therapy over metformin alone, while emphasizing the need for larger, long-term studies to confirm its safety, efficacy, and sustainability in diverse PCOS populations.

The possibility of a combination therapy (MET/LIRA) as an intervention in addressing metabolic and endocrine problems in PCOS

Research conducted by Sever et al. (2014), Hossain et al. (2023), and Xing et al. (2022) consistently demonstrates that combination therapy with liraglutide and metformin is more effective than metformin monotherapy. The two drugs appear to act synergistically by targeting both insulin resistance and weight-related metabolic dysfunction—such as elevated body weight and waist circumference—thereby reinforcing the combination's superior efficacy in improving anthropometric measures. In addition to weight reduction, these studies highlight that the combined regimen produces greater improvements in metabolic and endocrine outcomes. These include enhanced lipid profiles that raise high-density lipoprotein (HDL) cholesterol while lowering low-density lipoprotein (LDL) cholesterol and triglycerides (potentially by reducing the hepatic overproduction of very-low-density lipoprotein [VLDL]), alongside improved glycemic control. This dual action breaks the cycle of insulin resistance and hyperinsulinemia, leading to significant reductions in HOMA-IR and insulin levels (Hossain et al., 2023; Sever et al., 2014; Xing et al., 2022).

Women with PCOS treated with combination therapy also exhibited decreased insulin resistance and improved hormonal balance, characterized by reductions in total testosterone alongside regulatory shifts in gonadotropins like LH and FSH. This suggests broader therapeutic benefits, wherein attenuated androgen production helps normalize hypothalamic–pituitary–ovarian axis signaling compared to monotherapy (Jensterle et al., 2022; Xie et al., 2023). Despite these advantages, side effects such as nausea, diarrhea, and vomiting were reported, underscoring the importance of monitoring tolerability alongside efficacy. (Hossain et al., 2023; Jensterle Sever et al., 2014; Xing et al., 2022).

https://doi.org/10.24191/IJPNaCS.v9i1.10

5. CONCLUSION

This systematic review demonstrates that combination therapy with metformin and liraglutide produces superior outcomes compared to metformin monotherapy. This combination therapy demonstrated significant advantages in both metabolic and endocrine parameters, while also influencing the profile of associated adverse effects. Specifically, patients receiving combination therapy experienced greater reductions in body mass index (BMI), insulin resistance, and total testosterone levels than those treated with metformin alone (Hossain et al., 2023; Sever et al., 2014; Xing et al., 2022). However, these findings are based on a limited number of studies (n = 3) with a high risk of bias, which reduces confidence in the overall estimates of effect. Although combination therapy was associated with a higher incidence of gastrointestinal adverse effects, these were generally transient and manageable **(**Hossain et al., 2023; Sever et al., 2014). Further well-designed, large-scale, and long-term studies are needed to confirm these findings and to assess the durability of these benefits, including their potential impact on reproductive outcomes.

ACKNOWLEDGEMENTS/FUNDING

The authors would like to thank Mr. Vermont Arvesu, Acting Dean of the School of Pharmacy, for granting institutional permission and facilities support for this study. We also highly appreciate the invaluable mentorship, technical guidance, and editorial insights provided by our research advisers, Mr. Jebb Patrick Delos Santos, RPh, and Dr. Mac Ardy Gloria, RPh, MPH, PhD. Additionally, we thank the members of the review panel for their constructive comments and recommendations that helped improve the quality of this manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declared that they have no conflicts of interest to disclose.

AUTHORS' CONTRIBUTIONS

Ronna Nicole M. Tagalog: Supervision, Methodology, Formal analysis, Writing–original draft. **Leanne Christine S. Tantiado**: Visualization, Methodology, Writing – review & editing. **Jhedka C. Suñga**: Visualization, Resources, Draft corrections. **Frances Alyza A. Oclos**: Formal analysis, Methodology, review and editing. **Carl Jefferson E. Bernales:** Data Analysis, Data analysis, Writing – review & editing.

DECLARATION OF GENERATIVE AI IN THE WRITING PROCESS

During the preparation of this work, the authors used as an example of software such as ChatGPT (OpenAI) and Grammarly to improve language, grammar, and readability. All content was reviewed and edited by the authors, who take full responsibility for the final manuscript.

ETHICS STATEMENT

This study was reviewed by the Far Eastern University - Dr. Nicanor Reyes Medical Foundation Institutional Ethics Review Committee (FEU-NRMF IERC Protocol Code: FEU-NRMF IERC 2024-0126). Because this study was conducted as a systematic review of previously published literature and did not

involve direct contact with human participants, animal subjects, or prospective data collection, formal ethical approval and informed consent were deemed not applicable.

REFERENCES

American Society for reproductive Medicine. PCOS is now PMOS: Understanding the name change. Birmingham (AL): ASRM; 2026 May 27 (cited 2026 June 26). Available from: https://www.asrm.org/NEWS-AND-EVENTS/ASRM-NEWS/LATEST-NEWS/MAY-27-2026-PCOS-IS-NOW-PMOS-UNDERSTANDING-THE-NAME-CHANGE/

Christ, J. P., & Cedars, M. I. (2023). Current guidelines for diagnosing PCOS. *Diagnostics*, 13(6), Article 1113. https://doi.org/10.3390/diagnostics13061113

Cochrane. (2019). RoB 2: A revised Cochrane risk-of-bias tool for randomized trials. https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials

Deswal, R., Narwal, V., Dang, A., & Pundir, C. S. (2020). The prevalence of polycystic ovary syndrome: A brief systematic review. *Journal of Human Reproductive Sciences,* 13(4), 261-271. https://doi.org/10.4103/jhrs.JHRS_95_18

Hossain, A., Banu, H., Morshed, M. S., & Afrine, S. (2023). Short-term and low-dose liraglutide plus metformin decreased body mass index and insulin resistance more than metformin alone in obese women with polycystic ovary syndrome: An open-label randomized controlled study. *IMC Journal of Medical Science*, 18(1), 1-10. https://doi.org/10.55010/imcjms.18.002

Jensterle, M., Herman, R., & Janež, A. (2022). Therapeutic potential of glucagon-like peptide-1 agonists in polycystic ovary syndrome: From current clinical evidence to future perspectives. *Biomedicines*, 10(8), Article 1989. https://doi.org/10.3390/biomedicines10081989

Jensterle Sever, M., Kocjan, T., Pfeifer, M., Kravos, N. A., & 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. *European Journal of Endocrinology*, 170(4), 451-459. https://doi.org/10.1530/EJE-13-0797

Kumar, A. N., Naidu, J. N., Satyanarayana, U., Ravindran, K., & Anitha, M. (2016). Metabolic and endocrine characteristics of Indian women with polycystic ovary syndrome. *International Journal of Fertility and Sterility*, 10(1), 22-28. https://doi.org/10.22074/ijfs.2016.4764

Nylander, M., Frøssing, S., Clausen, H. V., Kistorp, C., Faber, J., & Skouby, S. O. (2017). Effects of liraglutide on ovarian dysfunction in polycystic ovary syndrome: A randomized clinical trial. *Reproductive BioMedicine Online*, 35(1), 121-127. https://doi.org/10.1016/j.rbmo.2017.03.023

PRISMA Executive. (2014). PRISMA statement. https://www.prisma-statement.org/prisma-executive

Shukla, A., Rasquin, L. I., & Anastasopoulou, C. (2025). Polycystic ovarian syndrome. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK459251/

Xie, X., Wu, C., Hao, Y., Wang, T., Yang, Y., Cai, P., Zhang, Y., Huang, J., Deng, K., Yan, D., & Lin, H. (2023). Benefits and risks of drug combination therapy for diabetes mellitus and its complications: A comprehensive review. *Frontiers in Endocrinology*, 14, Article 1301093. https://doi.org/10.3389/fendo.2023.1301093

Xing, C., Zhao, H., Zhang, J., & He, B. (2022). Effect of metformin versus metformin plus liraglutide on gonadal and metabolic profiles in overweight patients with polycystic ovary syndrome. *Frontiers in Endocrinology*, 13, Article 945609. https://doi.org/10.3389/fendo.2022.945609

https://doi.org/10.24191/IJPNaCS.v9i1.10