

Liraglutide plus Metformin versus Metformin alone in women living with Polyendocrine metabolic ovarian syndrome (PMOS): A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract:

Background: Polyendocrine metabolic ovarian syndrome (PMOS), formerly referred to as polycystic ovary syndrome (PCOS), is among the most common endocrine disorders in women of reproductive age. **Methods:** An extensive literature search was done on Cochrane, PubMed, TRIP and Google Scholar. Pooled effect estimates were calculated using a fixed-effect model ($I^2 < 0\%$) and a random-effects model was applied ($I^2 > 50\%$). **Result:** The combination of metformin and liraglutide was associated with significantly lower fasting blood glucose level as compared to mono-therapy [MD]= -0.19 mmol/L, 95% CI: -0.33-0.06 mmol/l, $Z=2.79$, $P=0.005$, $\chi^2=6.08$, $df=3$, $P=0.11$, $I^2=0\%$). The combination of drugs significantly increased sex hormone binding globulin as compared to monotherapy [MD]= 7.89L, 95% CI 3.80-11.99, $Z=3.78$, $P=0.0002$, $\chi^2=1.74$, $df=1$, $P=0.19$, $I^2=42\%$). The pooled analysis demonstrated that metformin significantly reduced the risk of nausea as compared to the Metformin and liraglutide combination (RR=8.30 95% CI: 2.64, 26.10, $Z=3.62$, $P=0.0003$, $\chi^2=0.43$, $df=2$, $p=0.80$, $I^2=0\%$). **Conclusion:** The combination of liraglutide and metformin was found to be advantageous over metformin in monotherapy, with respect to improving the patient's glycaemic control by inducing a significant reduction in the fasting blood glucose level as compared to monotherapy. The combination therapy also significantly increased sex hormone binding globulin, such hormonal control is an underpinning facet in the treatment of PMOS and therefore this finding advocates for the use of metformin and liraglutide in combination.

Keywords: Polycystic Ovary Syndrome, Sclerocystic Ovary Syndrome, Metformin Hydrochloride, Liraglutide

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Introduction

Polycystic ovarian syndrome (PCOS) has been formerly renamed and is now designated as Poly endocrine metabolic ovarian syndrome (PMOS). PMOS is one of the most common endocrine disorders in women within the reproductive age group. The updated guidelines for the diagnosis of PMOS demand other important etiologies and pathologies to be excluded as well as require two important features to be present: namely oligo- or anovulation. This must be coupled by clinical and or biochemical evidence of hyperandrogenism and polycystic ovarian sonographic evidence or an elevation in anti-Müllerian hormone levels [1,2].

PMOS is thus being viewed and treated as a disorder with multi systemic involvement which has various features which are at an interplay with one another and include endocrine malfunctions, including insulin resistance, hyperandrogenism and disrupted neuroendocrine regulation. Hyperinsulinemia, hyperandrogenism and impaired ovulation are among the endocrinological complications faced by individuals suffering from PMOS. PMOS is closely associated with higher BMI and obesity rates which further precipitate both the metabolic and reproductive dysfunction. Furthermore, obesity and an increased BMI drives the risk of type 2 diabetes mellitus, dyslipidemia, hypertension and cardiovascular disease higher. PMOS is intimately associated with fertility issues and often causes menstrual irregularities, chronic anovulation, adverse pregnancy outcomes as well as an elevated risk of gynecological malignancies. Besides the physiological disruptions caused by PMOS there is an added psychological aspect which patients face with many suffering from anxiety, depression as well as eating disorders [1,2].

The main modality used for the treatment of PMOS is life style modification with the main goal to restore ovulatory function and alleviate the diverse clinical manifestations of the disorder. In terms of medical drug management metformin has been widely used as the insulin-sensitizing agent of choice to improve the insulin resistance profile, glycemic control, lipid metabolism and ultimately has a role in the regulation of menstrual cycles [3-6].

With the development and wider use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), particularly liraglutide for its beneficial effects on appetite regulation, weight loss and insulin sensitivity. GLP-1 RAs are now also recommended as an adjunct to the lifestyle intervention to aid in the management of obesity in women with PMOS. The combination of liraglutide and metformin has shown a greater response in the improvement of anthropometric measures, insulin resistance and reproductive hormone profiles as when compared to mono therapy. [3,4,6].

Despite positive findings with the combination therapy, very little literature exists with tiny sample sizes. Therefore, this study aims to determine the true benefit of the combination therapy versus the dual therapy [7-10].

Methodology

Registration and Protocol

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines (PRISMA). The research protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number: CRD420261450113. The full protocol is available through the PROSPERO registry [11].

Search Strategy in various databases

An extensive literature search was done on Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Turning Research into Practice (TRIP) and Google Scholar to identify relevant RCTs published from 2014 to 2026. The search strategy combined MeSH (Medical Subheadings) terms, free text keywords, and Boolean operators. “Metformin” AND “Liraglutide” AND “Polycystic ovary syndrome” AND “Randomized Controlled Trials as Topic”. The detailed search strategy and number of records retrieved from each database employed are presented as shown in (Table 1).

Eligibility criteria

The eligibility criteria for this systematic review and meta-analysis were established using the PICOS framework (Population, Intervention, Comparison, Outcomes, Study design). The population comprised of patients diagnosed with Polyendocrine metabolic ovarian syndrome (PMOS). The intervention evaluated was a combination of Metformin and Liraglutide in the interventional group compared to Metformin in the control group. The outcomes were Glucose level, HOMA IR (Homeostatic model assessment of Insulin Resistance), BMI (Basal metabolic rate), Waist Circumference, VAT (Visceral adipose tissue), Insulin level, Testosterone levels, Sex hormone-binding globulin and Adverse Effects. The study design included Randomized Controlled Trials (RCTs) comparing a combination of Metformin and Liraglutide versus Metformin in women with PMOS.

Inclusion criteria

All Randomized Controlled Trials (RCTs) published between 2014 and 2026 that evaluated women diagnosed with polyendocrine metabolic ovarian syndrome (PMOS) or Polycystic Ovarian Syndrome (PCOD) were assessed and considered for inclusion in this study. Studies involving women diagnosed with polycystic ovarian syndrome or polyendocrine metabolic ovarian syndrome and comparing a combination of Metformin and Liraglutide versus Metformin

were eligible. Full-text articles published in English language were assessed and included in this systematic review and meta-analysis.

Exclusion criteria

Non-randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series, case reports, in vitro studies, animal experiments, commentaries, conference abstracts, editorials, letters to the editor, expert opinions, systematic reviews and review articles were excluded from the study.

Sample size Calculation

Sample size estimation was not performed, as this systematic review and meta-analysis aimed to include all eligible randomized controlled trials (RCTs) published during the predefined search period that met the inclusion criteria.

Data synthesis

The titles and abstracts were initially screened across various databases. The full texts of the examined RCT titles that met the eligibility requirements were considered for the final selection. All articles were screened independently by KM and IB and discrepancies were resolved by JR and IB (2).

Critical appraisal

The critical appraisal of the selected RCTs was assessed independently by two researchers IB and KM. The Cochrane risk-of-bias tool (RoB2) was used as a quality assessment tool for randomized trials. Any discrepancies between the reviewers were resolved through discussion until a consensus was reached [12].

The RoB2 tool is best suited and implemented to assess the domains at low, some concerns and high risk of bias. The Risk of Bias was assessed on five domains (D1-D5), which were as follows: D1: Bias arising from the randomization process, D2: Bias due to deviations from intended interventions, D3: Bias due to missing outcome data, D4: Bias in the measurement of the outcome, D5: Bias in selection of the reported result.

The Risk-of-bias Visualization (ROBVIS) tool is a web-based application program was used to develop the traffic light plots and the weighted bar plots [13].

Data analysis and Meta-analysis

Continuous outcomes were analyzed as mean difference (MD) with corresponding standard deviations, while dichotomous outcomes were expressed as risk ratios (RRs) with 95% Confidence intervals (CI). Pooled effect estimates were calculated using a fixed effect model when the statistical heterogeneity was low ($I^2 < 50\%$). A random effect model was applied when substantial heterogeneity was present ($I^2 > 50\%$). Statistical heterogeneity among studies

was assessed using the chi-square test. The degree of heterogeneity was assessed by using the I^2 statistic.

Statistical significance of the pooled estimates was determined by Z test, with p value < 0.05 considered statistically significant. Meta-analyses were performed, and forest plots were generated using the latest version of the Review Manager (RevMan Web) application (The Cochrane Collaboration, London, UK).

Results

An extensive literature search yielded a total of 431 articles (PubMed-14, Cochrane-13, TRIP-64, Google Scholar- 340). Among these, 299 were noted as duplicates and were excluded from the initial analysis by EndNote, 132 records marked as ineligible based on predetermined criteria. A total of 110 full-text articles were assessed for eligibility. 4 RCTs were finally assessed and were hence included for qualitative synthesis for systematic review and meta-analysis. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines are followed and implemented during the production of this systematic review (Figure 1).

Table 2 shows authors, study year, study design, country, and dose of combination of Metformin and Liraglutide vs Metformin. All the Studies are RCTs and have been conducted in Slovenia, United States and China. The dose of drugs used was Metformin 1000mg + Liraglutide 1.2mg QID (Sever et al., Salamun et al., Xing et al.) and Metformin 2000mg + Liraglutide 1.8mg QID (Elkind-Hirsch et al.) and the drug dose for Metformin was Metformin 1000mg BID (Sever et al., Salamun et al., Xing et al.) and Metformin 2000mg (Elkind-Hirsch et al.) [14-17].

Table 3 shows the frequency of menstrual cycle/number per year for both the intervention and control group as well as the BMI/Kg m^2 for the intervention as well as the control group (baseline vs after therapy values). The values for the frequency of menstrual cycle is given in the group. The BMI for interventional group ranged from 26.25 to 45.5 mmol/l for baseline and ranged from 23.49 to 39 mmol/after therapy. The BMI for control group ranged from 19.7 to 43.7 mmol/l for baseline and from 24.55 to 39.9 mmol/l after therapy.

Table 4 depicts the age of people living with PMOS in years and HOMA-IR for the combination of Metformin and Liraglutide vs Metformin. The age for the intervention group ranged from 18 to 45 years, and the age of the control group ranged from 18 to 45 years. The HOMA-IR of intervention group ranged from 1.4 to 6.94 for baseline and from 0.8 to 3.67 after treatment compared to the control group that

ranged from 1 to 7.6 for the baseline and from 0.85 to 4.91 after therapy.

Table 5 represents the glucose level and insulin level of women living with PMOS receiving the combination of Metformin and Liraglutide vs Metformin in monotherapy. The glucose level for the intervention group ranged from 4.3 to 8.3 mmol/l as baseline and from 4.3 to 9.6 mmol/l after therapy. The insulin level for both intervention and control group is given in the table.

Table 6 shows VAT Area/cm² for both intervention and control group and Waist Circumference/cm for intervention as well as control group (baseline vs after therapy values). The values for VAT Area/cm² ranged from 98.1 to 211.7 for the interventional group and from 84 to 205.4 for the control group. The Waist Circumference/cm for interventional group ranged from 86.75 to 139.6 before therapy and 78.05 to 134.8 after therapy. The Waist Circumference/cm for control group ranged from 79.87 to 123.3 for baseline and from 70.98 to 128.5 after therapy.

Table 7 shows the Total Testosterone along with SHBG (Sex Hormone Binding Globulin) in nmol/l. Values for Total Testosterone is given in the table. The values for SHBG (nmol/l)² ranged from 15.9 to 55.5 for the interventional group and from 22.6 to 49.4 for the control group.

Table 8 shows a list of adverse drug reactions for combination of Metformin and Liraglutide versus Metformin. The combination was found to cause more nausea, diarrhea as well as headaches than Metformin alone.

Risk of Bias Assessment

Four RCTs underwent a risk of bias evaluation using the RoB2 and Robvis visualisation tools. A traffic light plot (Figure 2a) and weighted bar plot (Figure 2 b) were developed. Overall risk of bias was low (n=2) and of some concern (n=2). Overall, the risk of bias assessment indicates that 50% of the included studies were at low risk of bias, while 50% had some concerns. All studies demonstrated low risk of bias arising from the randomization process, deviations from intended interventions, and missing outcome data. Some concerns were identified in the measurement of outcomes and selection of the reported results in two studies. No study was judged to have a high overall risk of bias.

Meta- analysis

A fixed-effect meta-analysis of four randomized controlled trials involving 176 participants (86 receiving metformin and liraglutide) and 90 receiving metformin alone. The pooled analysis showed no statistically significant difference in age between the two groups mean difference [MD] = 0.85 years

and 95% confidence interval [CI]: -0.92- 2.62, $z=0.94$, $P=0.35$. There was no evidence of significant heterogeneity among the included studies (Chi square=2.90, $df=3$, $p=0.41$, $I^2=0\%$). Overall, the baseline age of the participants was comparable between metformin and liraglutide and metformin monotherapy groups (Figure 3.1). A random-effects meta-analysis of four RCTs involving 176 participants demonstrated that the combination of metformin and liraglutide was associated with significantly lower fasting blood glucose level compared to monotherapy [MD]= -0.19 mmol/L, 95% CI: -0.33-0.06 mmol/l, $Z=2.79$, $P=0.005$). There was no significant heterogeneity among the included studies (Chi-square=6.08, $df=3$, $P=0.11$, $I^2=0\%$), indicating highly consistent findings across studies. Overall, the evidence suggests that the metformin and liraglutide combination is more effective than metformin alone in reducing fasting blood glucose levels (Figure 3.2). Figure 3.3 represents a random-effects meta-analysis of four RCTs involving 176 participants demonstrated no statistically significant difference in BMI between the metformin and liraglutide combination and Metformin alone [MD]= (0.32kg/m², 95% CI- -0.90-1.53, $P=0.61$, $Chi^2 = 3.53$, $df = 3$, $P = 0.32$, $I^2=15\%$). The low heterogeneity indicates consistent results across studies. The pooled analysis showed no statistically significant difference in HOMA IR between the two groups [MD]=-0.18, 95% CI: -0.72-0.35, $z=0.67$, $p=0.51$, chi square=0.02, $df=1$, $p=0.87$, $I^2=0\%$) (Figure 3.4). The pooled analysis showed no statistically significant difference in waist circumference between the two groups [MD]=1.67 cm, 95% CI: -1.99-5.33 cm, $z=0.90$, $p=0.37$, chi square=2.61, $df=3$, $p=0.46$, $I^2=0\%$) (Figure 4.1). Figure 4.2 shows a fixed effect model meta-analysis involving two RCTs showed no significant difference in visceral adipose tissue area between metformin and liraglutide combination and metformin monotherapy (MD= 0.98 cm, 95 % CI -26.01 , 27.97, $Z = 0.07$, $P = 0.94$, $Chi^2 = 0.02$, $df = 1$, $P = 0.88$, $I^2 = 0\%$). A random-effects meta-analysis of two randomized controlled trials involving 79 participants found no statistical differences in fasting insulin levels between two groups [MD]= 15.31, 95 % CI: -34.97-65.59, $Z=0.60$, $P=0.55$. Moderate heterogeneity was observed across studies (Chi square=2.42, $df=1$, $p=0.012$, $I^2=59\%$). Overall, the available evidence suggests that the combination therapy with metformin and liraglutide does not significantly improve fasting insulin levels as compared to metformin monotherapy (Figure 4.3). A random effects meta-analysis of three RCTs involving 104 participants showed no statistical differences in total testosterone levels between two

groups [MD]= -0.09nmol/l, 95 % CI: -0.59-0.41nmol/l, Z=0.36, P=0.72). Moderate heterogeneity was observed across studies (Chi square=5.67, df=2, p=0.06, I²=64%). Overall, the available evidence suggests that the combination therapy with metformin and liraglutide does not significantly improve total testosterone as compared to metformin monotherapy alone. (Figure 4.4)

A fixed effects meta-analysis of two RCTs involving 79 participants demonstrated that the combination of metformin and liraglutide significantly increased sex hormone binding globulin as compared to monotherapy [MD]= 7.89L, 95% CI 3.80-11.99, Z=3.78, P=0.0002). There was low heterogeneity among the included studies (Chi-square=1.74, df=1, P=0.19, I²=42%), indicating consistent findings across studies. Overall, the evidence suggests that the metformin and liraglutide combination is more effective than metformin alone in increasing Sex hormone-binding globulin levels (Figure 5.1). A meta-analysis of three RCTs involving 124

participants evaluated nausea adverse effects associated with combination of metformin and liraglutide and metformin as monotherapy. The pooled analysis using a fixed effect Mantel Haenszel model demonstrated that metformin significantly reduced the risk of nausea compared to Metformin and liraglutide combination (RR=8.30 95% CI: 2.64, 26.10, Z=3.62, P=0.0003). Chi square=0.43, df=2, p=0.80, I² =0%). These findings suggest that the combination of metformin and liraglutide increases the risk of nausea than Metformin as monotherapy. (Figure 5.2). The risk of diarrhoea did not differ significantly between the metformin and liraglutide combination and Liraglutide monotherapy (RR=2.21, 95% ci 0.28-17.31, p=0.45). Significant heterogeneity was observed across trials (I²=72%). (Figure 5.3)

Table 1: Search Strategy and MeSH terms/ Databases used

Date and time of search	Database Used	MeSH terms used	Filters Used	Number (n)
02/08/26 at 22:15	PubMed	(((((((((Metformin[Title/Abstract]) OR (HCl, Metformin[Title/Abstract])) OR (Metformin HCl[Title/Abstract])) OR (Hydrochloride, Metformin[Title/Abstract])) OR (Metformin Hydrochloride[Title/Abstract])) OR (Glucophage[Title/Abstract])) OR (Dimethylguanylguanidine[Title/Abstract])) OR (Dimethylbiguanidine[Title/Abstract])) AND ((((((Liraglutide) OR (Saxenda)) OR (Victoza)) OR (NN2211)) OR (NN-2211)) OR (NN 2211))) AND (((((((((((Polycystic Ovary Syndrome) OR (Sclerocystic Ovary)) OR (Ovary, Sclerocystic)) OR (Sclerocystic Ovaries)) OR (Syndrome, Stein-Leventhal)) OR (Stein Leventhal Syndrome)) OR (Stein-Leventhal Syndrome)) OR (Sclerocystic Ovary Syndrome)) OR (Ovarian Degeneration, Sclerocystic)) OR (Sclerocystic Ovarian Degeneration)) OR (Polycystic Ovary Syndrome 1)) OR (Ovarian Syndrome, Polycystic)) OR (Polycystic Ovarian Syndrome)) OR (Syndrome, Polycystic Ovary)) OR (Ovary Syndrome, Polycystic))) AND (((Randomized Controlled Trials as Topic) OR (Controlled Clinical Trials, Randomized)) OR (Trials, Randomized Clinical)) OR (Clinical Trials, Randomized))	English, Humans, From 2014 to 2026	14
02/08/26 at 22:22	Cochrane	MeSH descriptor:[Polycystic Ovary Syndrome] explode all trees OR MeSH descriptor:[metformin] explode all trees OR MeSH descriptor:[liraglutide] explode all trees	From 2014 to 2026	13
02/08/26 at 22:30	TRIP	Polyendocrine metabolic ovarian syndrome OR PMOS OR Polycystic Ovarian Syndrome OR PCOS AND Liraglutide OR GLP-1 OR Glucagon like Peptide-1 OR Metformin OR Biguanides	From 2014 to 2026	64
02/08/26 at 22:35	Google scholar	Polyendocrine metabolic ovarian syndrome OR PMOS OR Polycystic Ovarian Syndrome OR PCOS AND Liraglutide OR GLP-1 OR Glucagon like Peptide-1 OR Metformin OR Biguanides	From 2014 to 2026	340
TOTAL				n=431

Table 2: Study Characteristics

Author, study year	Study Design	Sample size	Country	Intervention	Control	Comments	Dose of the intervention group	Dose of control group
Sever et al., 2014 [14]	RCT	25	Slovenia	Metformin and Liraglutide combination N=11	Metformin N=14		Metformin 1000mg + Liraglutide 1.2mgQID	Metformin 1000mg BID
Salamun et al., 2018 [15]	RCT	27	Slovenia	Metformin and Liraglutide combination N=13	Metformin N=14		Metformin 1000mg + Liraglutide 1.2mgQID	Metformin 1000mg BID
Elkind-Hirsch et al., 2020 [16]	RCT	72	United States	Metformin and Liraglutide combination N=35	Metformin N=37	Combination of metformin and placebo was used	Metformin 2000mg + Liraglutide 1.8mgQID	Metformin 2000mg
Xing et al., 2022 [17]	RCT	52	China	Metformin and Liraglutide combination N=27	Metformin N=25		Metformin 1000mg + Liraglutide 1.2mgQID	Metformin 1000mg BID

Table 3: Frequency of menstrual cycle/number per year and the BMI/Kg m²

Author, study year	Frequency of menstrual cycle/number per month		BMI/Kg m ²			
	Interventional group	Control Group	Baseline for interventional group	After Therapy for interventional group	Baseline for control group	After Therapy for control group
Sever et al., 2014 [14]	0.7± 0.3 (n per month)	0.6± 0.4 (n per month)	37.6± 5.1	35.3 ± 5.5	36.6 ± 3.5	36.1 ± 3.8
Salamun et al., 2018 [15]	NA	NA	37.8 ± 3.0	35.1 ± 3.5	35.5 ± 4.9	33.0 ± 3.3
Elkind-Hirsch et al., 2020 [16]	NA	NA	37.2 ± 8.3	33.8 ± 5.2	33.8 ± 5.2	32.8 ± 6.0
Xing et al., 2022 [17]	92.59% (25) (%n)	88% (22) (%n)	29.69 ± 3.44	26.24 ± 2.75	28.80 ± 4.25	26.88 ± 3.76

NA: Not available

Table 4: Age of people living with PMOS in years and HOMA-IR

Author	Age/years		HOMA-IR score			
	Interventional group	Control Group	Interventional group Baseline	Interventional group After treatment	Control group Baseline	Control group After treatment
Sever et al., 2014[14]	31.1 ± 5.1	31.3 ± 9.4	1.7(4.9)	2.1(2.9)	3.8(3.8)	2.5(2.4)
Salamun et al., 2018 [15]	30.1 ± 3.6	31.1 ± 4.7	NA	NA	NA	NA
Elkind-Hirsch et al., 2020 [16]	31.5 ± 13.5	31.5 ± 13.5	2.6 ± 1.2	2.2 ± 1.4	2.4 ± 1.4	2.35 ± 1.5
Xing et al., 2022 [17]	25.85 ± 4.45	23.52 ± 4.65	4.85 ± 2.09	2.62 ± 1.05	4.53 ± 3.07	2.86 ± 2.05

NA: Not available

Table 5: Glucose level and insulin level of women living with PMOS

Author	Glucose level		Insulin level	
	Interventional group	Control group	Interventional group	Control group
Sever et al., 2014 [14]	5.8 ± 1.3 (mmol/l)	7.6 ± 2.0 (mmol/l)	56.8(73.2) mU/L	86.9(75.3) mU/L
Salamun et al., 2018 [15]	6.3 ± 2.0 (mmol/l)	6.6 ± 2.3 (mmol/l)	124.4 ± 123.4(mU/L)	69.4 ± 43.0 (mU/L)
Elkind-Hirsch et al., 2020 [16]	4.9 ± 0.36 (mmol/l)	5.1 ± 0.47 (mmol/l)	NA	NA
Xing et al., 2022 [17]	5.05 ± 0.40 (mmol/l)	5.20 ± 0.32 (mmol/l)	11.60 ± 4.22 (μU/ml)	12.87 ± 7.93 (μU/ml)

NA: Not available

Table 6: VAT and Waist Circumference of women living with PMOS

Author	VAT Area/cm ²		Waist Circumference/cm			
	Interventional group	Control Group	Interventional group Baseline	Interventional group After treatment	Control group Baseline	Control group After treatment
Sever et al., 2014[14]	154.9 ± 56.8	151.9 ± 35.6	121.9 ± 17.7	116.4 ± 18.4	122.3 ± 7.0	120.7 ± 7.8
Salamun et al., 2018 [15]	143.7± 38.1	144.7 ± 60.7	114.5 ± 9.9	102.8 ± 9.3	108.8 ± 14.5	97.5 ± 11.0
Elkind-Hirsch et al., 2020 [16]	NA	NA	100.3 ± 13.2	94.3 ± 15.2	96.4 ± 12.2	95.3 ± 15.2
Xing et al., 2022 [17]	NA	NA	95.69 ± 8.94	86.30 ± 8.25	91.96 ± 12.09	83.40 ± 12.42

Table 7: Total testosterone along with SHBG (Sex Hormone Binding Globulin) of women living with PMOS

Author, study year	Total Testosterone		SHBG (nmol/l)	
	Interventional group	Control group	Interventional group	Control group
Sever et al., 2014[14]	1.6 ± 0.7 (nmol/l)	1.5 ± 0.9 (nmol/l)	44.0(31.0)	24.0(11.0)
Salamun et al., 2018 [15]	1.5 ± 0.6 (nmol/l)	1.3 ± 0.5 (nmol/l)	35.7 ± 19.8	36.0 ± 13.4
Elkind-Hirsch et al., 2020 [16]	NA	NA	NA	NA
Xing et al., 2022 [17]	2.15± 0.83 (nmol/l)	2.74 ± 1.07 nmol/l)	33.75 ± 11.15	24.93 ± 2.53

NA: Not available

Table 8: Adverse drug reactions for the combination of Metformin and Liraglutide versus Metformin.

Author	ADR	
	Combination of Metformin and liraglutide	Metformin
Sever et al.,2014 [14]	Nausea 6/11 and Diarrhea 6/11 headache (3/11), insomnia (2/11)	Nausea 1/14 and Diarrhea 1/14 Hypoglycemia 1/14
Salamun et al.,2018 [15]	Nausea 5/13	Diarrhea 1/14
	Headache 2/13	Nausea 1/14
Elkind-Hirsch et al.,2020 [16]	Nausea 13/35 (37.2%)	Nausea 1/37 (2.7%)
	Diarrhea 6/35 (18.0%)	Diarrhea 7/37 (17.3%)
Xing et al.,2022 [17]	NA	NA

NA: Not available

Figure 1: PRISMA 2020 flowchart

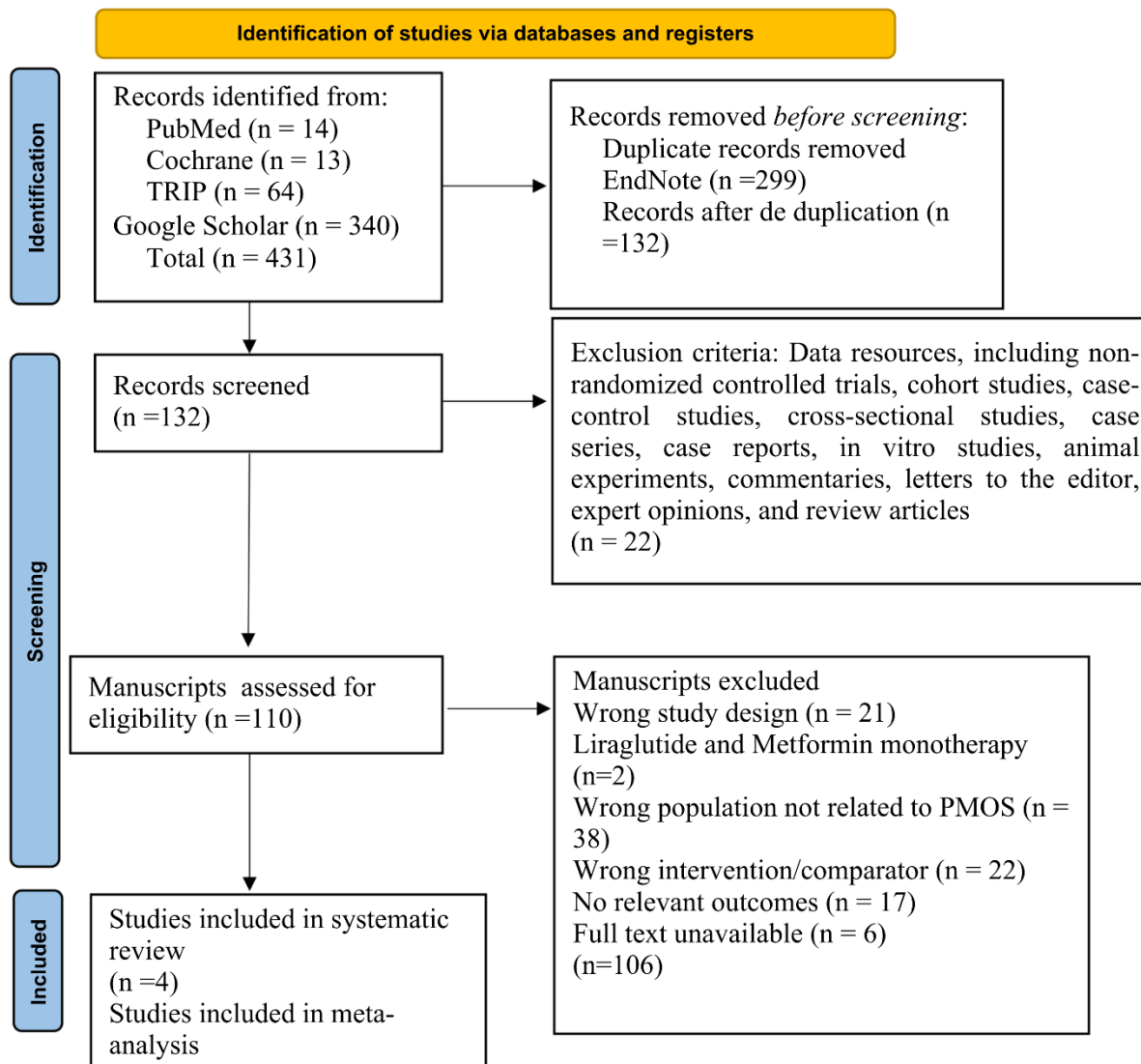


Figure 2 Risk of Bias: Traffic Light Plot for Risk of Bias (a) and Weighted Bar plot for Risk of Bias Analysis (b)

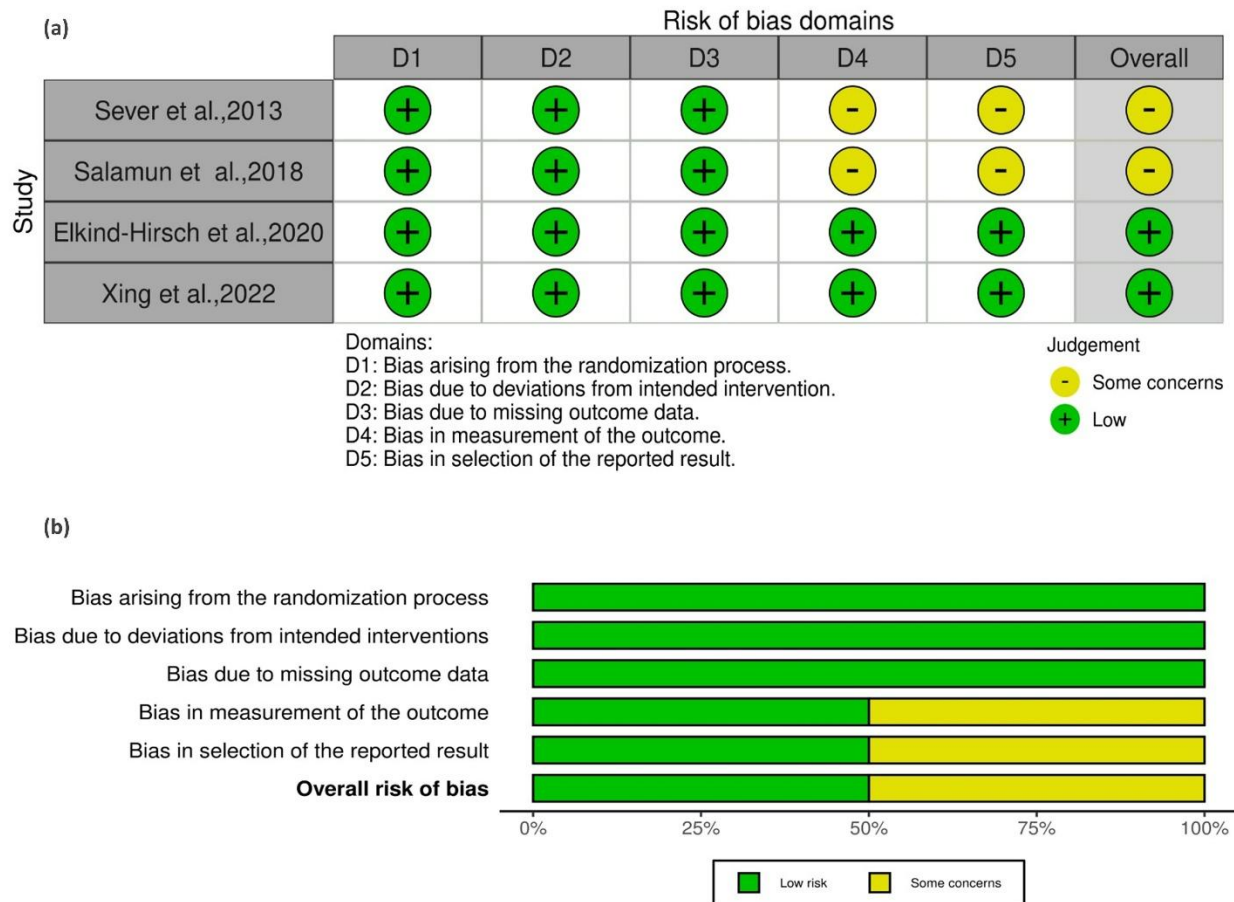


Figure 3: Forest plots of patients receiving a combination of metformin and liraglutide and Metformin in PMOS, Age (3.1), Glucose level (3.2), BMI (3.3), Homeostatic model assessment of Insulin Resistance (3.4)

Figure 3.1 (Age)

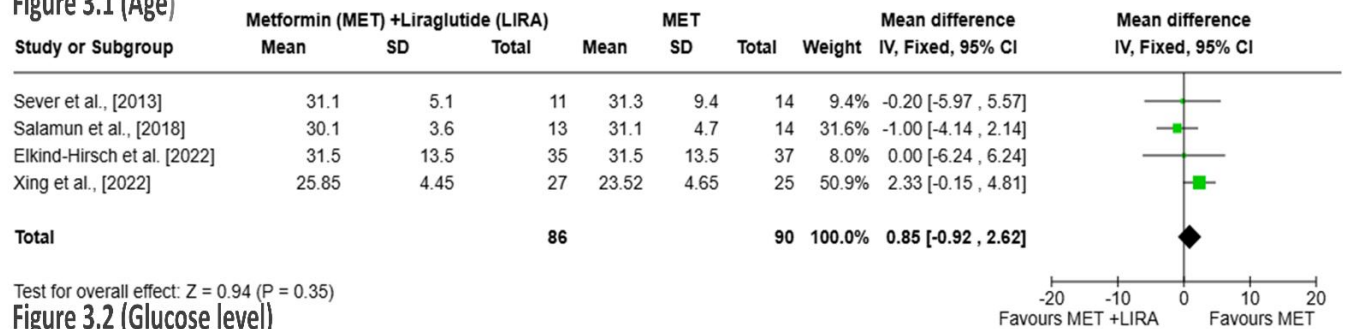
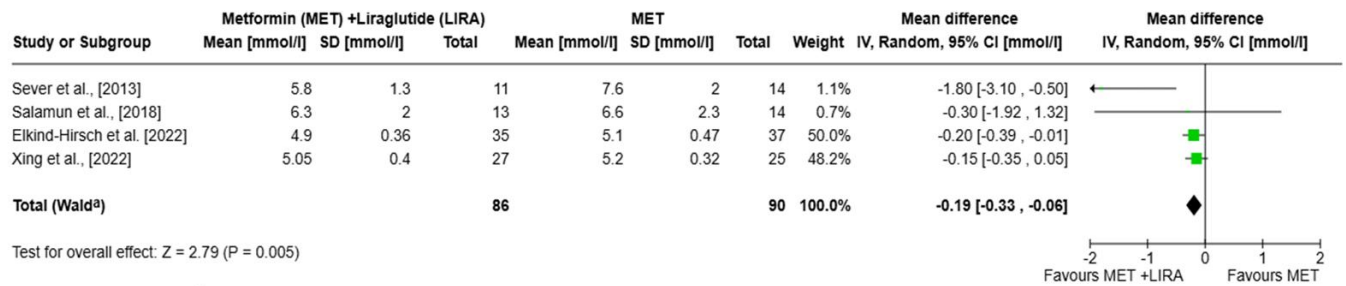


Figure 3.2 (Glucose level)

Heterogeneity: $\text{Chi}^2 = 2.90$, $df = 3$ ($P = 0.41$); $I^2 = 0\%$



Footnotes

^aCI calculated by Wald-type method.

^b Tau^2 calculated by Restricted Maximum-Likelihood method.

Figure 3.3 (BMI)

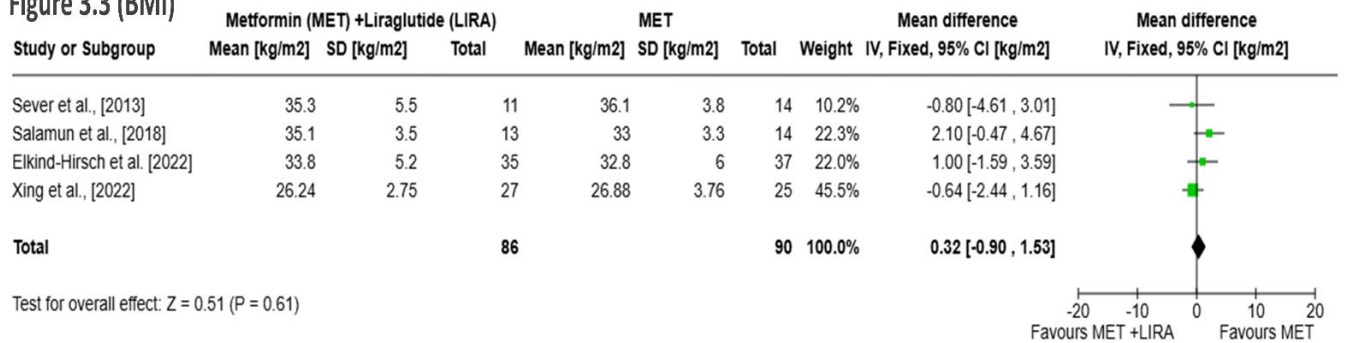


Figure 3.4 (HOMA IR)

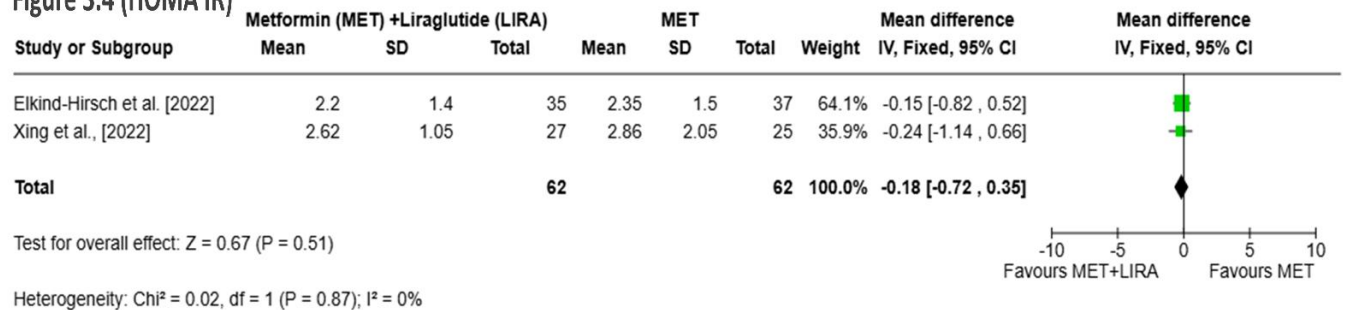


Figure 4: Forest plots of patients who received a combination of metformin and liraglutide and Metformin in PMOS, Waist Circumference (4.1), Visceral adipose tissue (4.2), Insulin (4.3), Testosterone level (4.4)

Figure 4.1 (Waist Circumference)

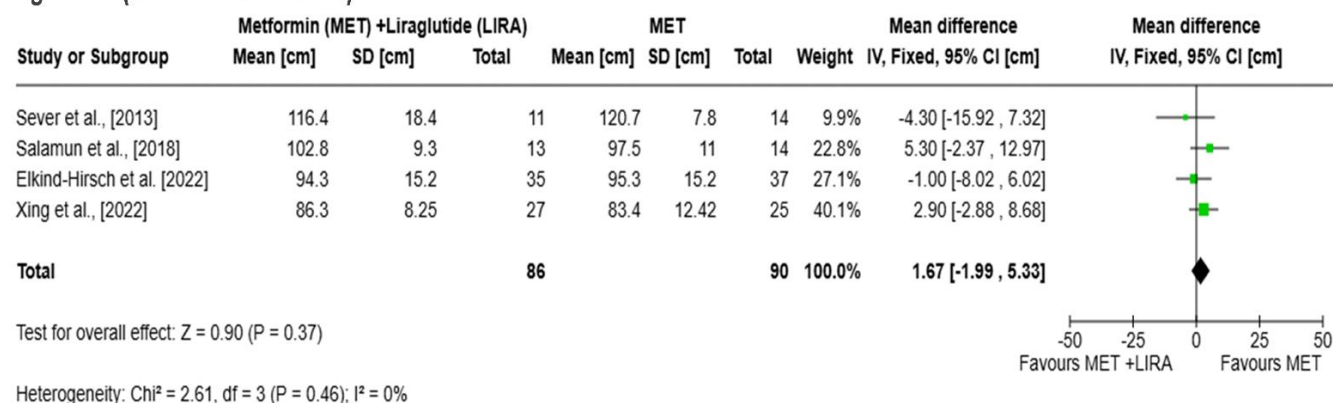


Figure 4.2 (VAT)

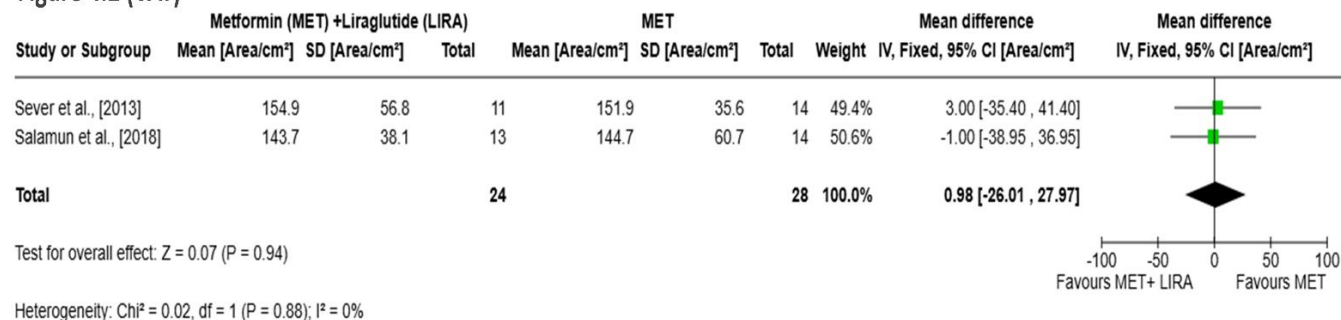
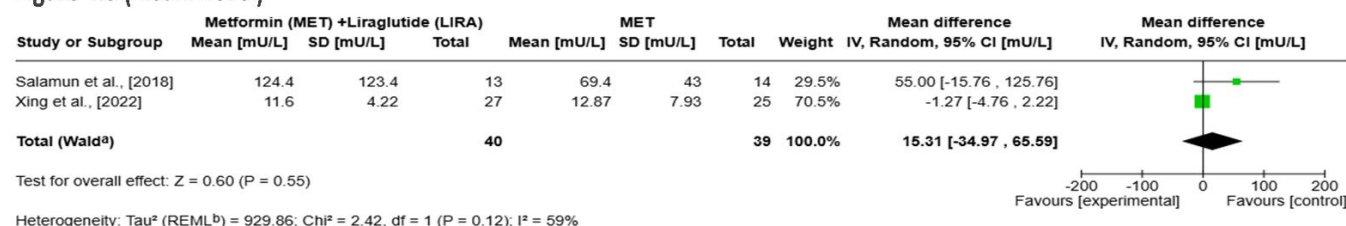


Figure 4.3 (Insulin level)

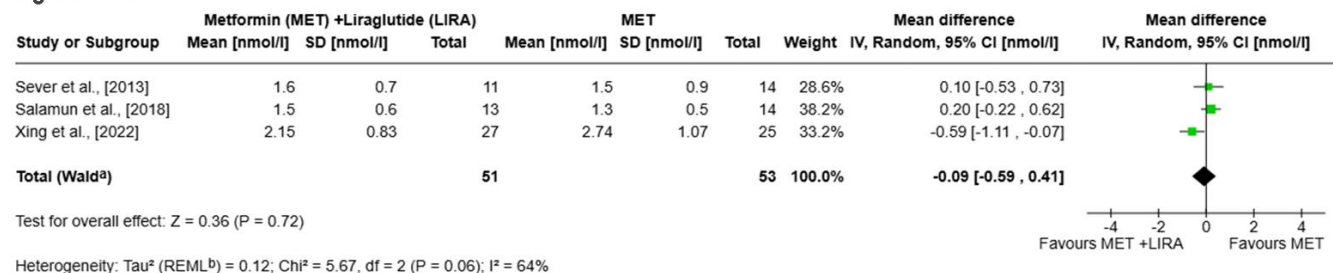


Footnotes

^aCI calculated by Wald-type method.

^bTau² calculated by Restricted Maximum-Likelihood method.

Figure 4.4 Testosterone



Footnotes

^aCI calculated by Wald-type method.

^bTau² calculated by Restricted Maximum-Likelihood method.

Figure 5: Forest plots of Sex hormone-binding globulin (5.1), adverse effects, nausea (5.2), diarrhoea (5.2) of the patients who received a combination of metformin and liraglutide and Metformin in PMOS

Figure 5.1 Steroid-binding globulin

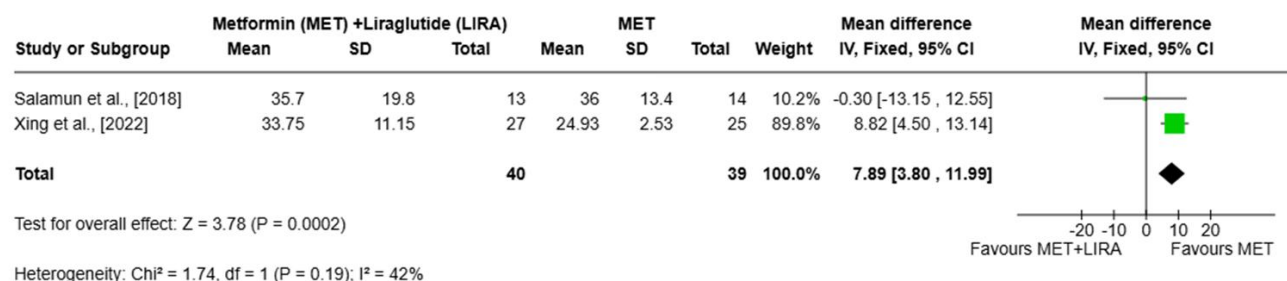


Figure 5.2 Nausea

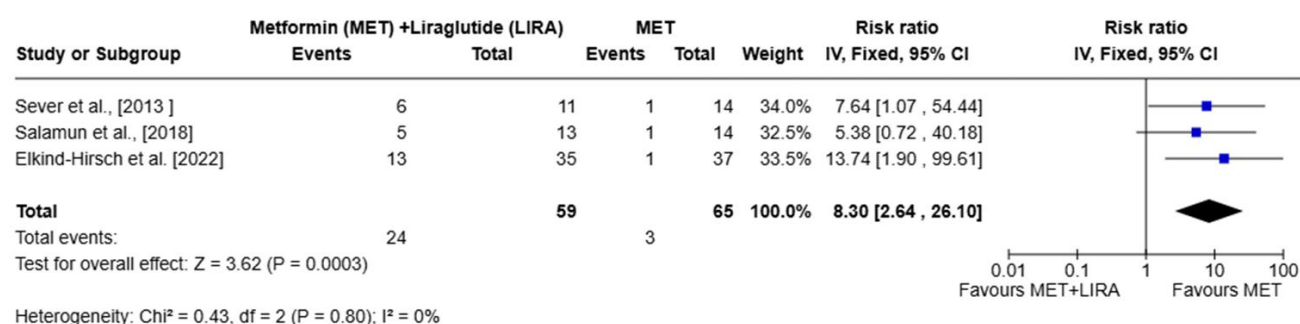
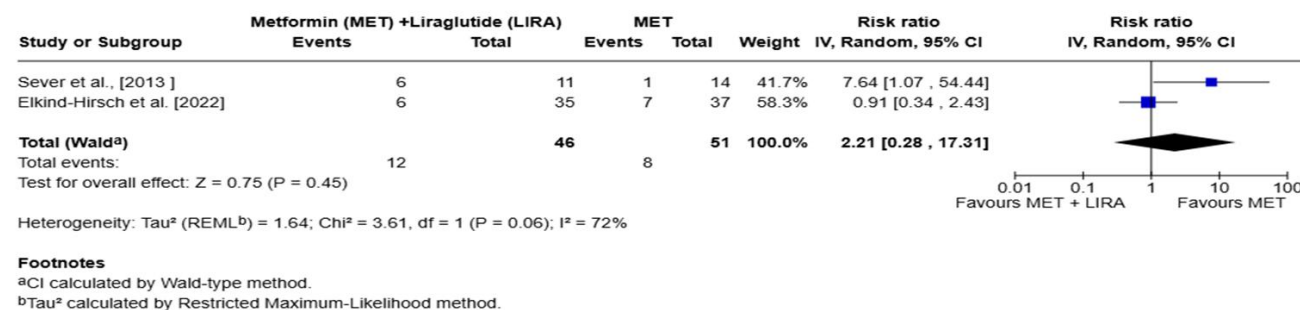


Figure 5.3 Diarrhoea



Discussion

This systematic review and meta-analysis evaluated the comparative efficacy of the combination therapy of metformin and liraglutide vs metformin monotherapy in women with polyendocrine metabolic ovarian syndrome (PMOS). After an extensive literature review, four randomized controlled trials were used to determine whether the combination will be the

novel breakthrough in the treatment of PMOS. This study is pertinent because of two important factors: firstly, liraglutide is a GLP-1 receptor agonist and currently the use of such peptides has exploded globally with these medications being used for a wide array of off-label uses, with remarkable and sometime life changing effects, in stark contrast to this the novelty of these drugs means that new adverse effects are being identified on a continuous basis [18]. Secondly, Polyendocrine metabolic

ovarian syndrome (PMOS), formerly referred to as polycystic ovary syndrome (PCOS), is among the most common endocrine disorders in women of reproductive age, affecting an estimated 11–13% of this population globally, impacting approximately one in eight women. PMOS is a multisystem disorder driven by complex endocrine abnormalities, involving insulin signaling, hyperandrogenism, ovarian function and disrupted neuroendocrine regulation [19,20] Liraglutide is structurally analogous to human GLP-1 with a 97% homology and has demonstrated potent antidiabetic properties, distinguished by its extended half-life and enhanced stability, [21] while metformin has traditionally been used in the treatment of PMOS due to its insulin enhancing action. The synergistic pharmacological action of metformin and Liraglutide is important in the management of PMOS [22]. This study has discovered three important and statistically significant findings in respect to glycaemic control, hormonal control as well as drug tolerability.

Glycaemic control

The random-effects meta-analysis of four RCTs involving 176 participants demonstrated that the combination of metformin and liraglutide was associated with significantly lower fasting blood glucose level as compared to monotherapy [MD]= -0.19 mmol/L, 95% CI: -0.33-0.06 mmol/l, Z=2.79, P=0.005). There was no significant heterogeneity among the included studies (Chi-square=6.08, df=3, P=0.11, I²=0%), indicating highly consistent findings across studies. Overall, the evidence suggests that the metformin and liraglutide combination is more effective than metformin alone in reducing fasting blood glucose levels. The underlying mechanism may reflect a synergistic pharmacological action of metformin and Liraglutide [14-17]. Metformin reduces blood glucose in type two diabetes mellitus (T2DM) by enhancing the action of insulin mainly through activation of the adenosine monophosphate activated protein kinase (AMPK) pathway. While Liraglutide, a GLP-1 receptor agonist, promotes glucose dependent insulin secretion delays gastric emptying and exerts central appetite suppressing effect leading to improved glycaemic profiles. This systematic review and metanalysis has therefore proven that the combination of metformin and liraglutide through their differing mechanism of actions ultimately target and improve one of the underpinning pathologies (poor glycaemic control) in PMOS [14-17].

Hormonal control

A fixed effects meta-analysis of two RCTs conducted by Salamun et al. and Xing et al. involving 79 participants demonstrated that the combination of metformin and liraglutide significantly increased sex hormone binding globulin as compared to monotherapy [MD]= 7.89L, 95% CI 3.80-11.99, Z=3.78, P=0.0002) [15, 17]. There was low heterogeneity among the included studies (Chi-square=1.74, df=1, P=0.19,

I²=42%), indicating consistent findings across studies. Overall, the evidence suggests that the metformin and liraglutide combination is more effective than metformin alone in increasing Sex hormone-binding globulin levels. The level of sex hormone binding globulin (SHBG) was significantly increased in those using the combination therapy vs monotherapy. This is a positive impact as an increase in SHBG in the body means that free testosterone is reduced in the body. In contrast to this finding a random-effects meta-analysis of three of the included RCTs involving 104 participants showed no statistical differences in total testosterone levels between the two groups [MD]= -0.09nmol/l, 95 % CI: -0.59-0.41nmol/l, Z=0.36, P=0.72). Moderate heterogeneity was observed across studies (Chi square=5.67, df=2, p=0.06, I²=64%). It could be due to differences in the treatment duration across the included RCTs.

Overall, the available evidence suggests that the combination therapy with metformin and liraglutide does not significantly improve total testosterone as compared to metformin monotherapy. The above findings are both supported and contradicted by the findings of a study performed in Greece by Livadas S, et al. [23]. In which all of the participants showed a statistically significant decrease of insulin resistance index HOMA-IR, and androgen levels, with significant improvement of fat deposition, menstrual cycle pattern and the degree of hirsutism was disclosed (P<0.05 for all comparisons). Hormonal control is an underpinning facet in the treatment of PMOS and therefore this finding strongly advocates for the use of metformin and liraglutide in combination [23].

Tolerability

A meta-analysis of three randomized controlled trials performed by Salamun et al. Sever et al. and Elkind-Hirsch et al. involving 124 participants evaluated the adverse effects associated with the combination of metformin and liraglutide in comparison to metformin as a monotherapy [14-16]. The pooled analysis using a fixed-effect Mantel-Haenszel model demonstrated that metformin significantly reduced the risk of nausea as compared to the Metformin and liraglutide combination (RR=8.30 95% CI: 2.64, 26.10, Z=3.62, P=0.0003). Chi square=0.43, df=2, p=0.80, I²=0%). These findings suggest that the combination of metformin and liraglutide increases the risk of nausea as opposed to Metformin as a monotherapy. The risk of diarrhoea did not differ significantly between the metformin and liraglutide combination and Liraglutide monotherapy (RR=2.21, 95% CI 0.28-17.31, p=0.45). Significant heterogeneity was observed across trials (I²=72%). A study performed in China by Wu H, et al. supports the notion that various underlying contributory factors such as Alpha-glucosidase inhibitor (AGI), concomitant gastrointestinal diseases, female sex and higher TSH levels are independent risk

factors of gastrointestinal side effects of liraglutide treatment in patients with type 2 diabetes [24].

BMI

A random-effects meta-analysis of all four of the randomised controlled trials involving 176 participants demonstrated no statistically significant difference in BMI between the metformin and liraglutide combination and Metformin alone [MD]= (0.32kg/m², 95% CI- -0.90-1.53, P=0.61, Chi² = 3.53, df = 3, P = 0.32, I²=15%). The low heterogeneity indicates consistent results across studies [14-17]. This finding is notable as one of the uses of Liraglutide internationally and part of why the drug's use has exploded so dramatically is due to its popularity as a weight loss agent. Furthermore, this systematic review and meta-analysis did not demonstrate a statistically significant difference in HOMA-IR levels (Homeostatic model assessment of Insulin Resistance), insulin levels, waist circumference, and VAT area (Visceral adipose tissue).

The findings of this study are both statistically and clinically significant and can aid both policy makers, drug agencies as well as treating physicians in managing patients with PMOS. The low heterogeneity across both the significant and insignificant findings indicates consistent results across the relevant randomized controlled trials included in this meta-analysis and therefore further bolsters and strengthens this study's findings.

Limitation

The main limitation of this study is that only 4 RCTs were found to be eligible and were included in this systematic review and meta analysis. In future more long term multicentric trials with larger sample size are required to validate these findings on reproductive outcomes and safety profile.

Conclusion

The systematic review and meta analysis showed that the combination of liraglutide and metformin was found to be advantageous over metformin in monotherapy, with respect to improving the patients glycaemic control by inducing a significant reduction in the fasting blood glucose level as compared to monotherapy. The combination therapy also significantly increased sex hormone binding globulin, such hormonal control is an underpinning facet in the treatment of PMOS and therefore this finding strongly advocates for the use of metformin and liraglutide in combination. Despite this, the combination of the two agents does induce more side effects as compared to metformin monotherapy. The combination of the two agents shows an improved control of PMOS in important clinical domains and its therefore pertinent that further studies are conducted in order to better understand the combination and to identify the optimized dosing schedule in order to reduce the side effect profile.

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Quality assessment: KM, IB

Data analysis: KM, IB

Drafting Original draft: IB, KM, JR, NP, SB, VDY, O-T OL, IB (2)

Editing and Critical Review: IB, KM, JR, NP, SB, VDY, O-T OL, IB (2)

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Competing interests

There is no conflict of interest between any of the authors.

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