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Original Article

Clinical efficacy of liraglutide combined with pioglitazone in obese polycystic ovary syndrome and its effects on the serum chemerin/visfatin ratio

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Abstract: Objective: To evaluate the clinical efficacy and safety of liraglutide combined with pioglitazone in obese patients with polycystic ovary syndrome (PCOS), and to explore the predictive value of serum chemerin, visfatin and their ratio for the improvement of insulin resistance (IR). Methods: A total of 338 obese PCOS women enrolled in this retrospective study were divided into two groups. The control group (n=168) received pioglitazone alone (15-30 mg/day), while the combination group (n=170) received liraglutide (0.6-1.8 mg/day) plus pioglitazone for 24 weeks. Anthropometric, metabolic, hormonal and adipokine-related indicators were compared before and after treatment. Correlation analysis, ROC curve analysis and multivariate logistic regression analysis were subsequently performed. Results: After treatment, the combination group exhibited significantly better improvements in multiple anthropometric, metabolic, hormonal and adipokine parameters than the control group (all P<0.001). The overall clinical response rate was markedly higher in the combination group (92.35% vs. 78.57%, P<0.001), whereas the incidence of adverse events showed no significant between-group difference (P=0.628). Baseline HOMA-IR was positively correlated with chemerin (r=0.569), visfatin (r=0.360) and chemerin/visfatin ratio (r=0.580) (all P<0.001). The chemerin/visfatin ratio yielded the highest predictive efficiency for IR improvement, with an AUC of 0.703. Multivariate logistic regression identified treatment regimen (OR=4.858), baseline chemerin/visfatin ratio (OR=1.281), BMI (OR=1.169), triglycerides (OR=1.874) and testosterone (OR=2.997) as independent influencing factors for IR improvement (all P<0.05). No significant interaction was observed between treatment regimen and baseline chemerin/visfatin ratio or BMI. Conclusion: Liraglutide combined with pioglitazone can effectively ameliorate body mass, glucose and lipid metabolism, reproductive hormone levels and IR in obese PCOS patients, without increasing the risk of adverse events. The serum chemerin/visfatin ratio is closely correlated with IR and may serve as a promising biomarker for predicting treatment response in obese PCOS.

Keywords: Polycystic ovary syndrome, liraglutide, pioglitazone, insulin resistance, chemerin, visfatin

Introduction

Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrine and metabolic disorders affecting women of reproductive age, with a reported prevalence ranging from 5% to 20%. It is clinically characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology on ultrasonography [1]. Accumulating evidence indicates that PCOS originates from the interplay of genetic predisposition, environmental exposure and unhealthy lifestyle, and is currently recognized as a complex multisystem disorder [2]. Nearly half of PCOS patients are overweight or obese. This obese phenotype is accompanied by a higher incidence of glucose and lipid metabolic disturbances, as well as elevated cardiovascular disease risk [3].

Insulin resistance (IR) is widely acknowledged as the core pathological mechanism underlying

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PCOS and plays a pivotal role in disease progression [4]. Approximately 75% of women with PCOS present with varying degrees of insulin resistance. IR can trigger compensatory hyperinsulinemia, which further stimulates ovarian androgen overproduction, thereby aggravating hyperandrogenism and ovulatory dysfunction [5]. Notably, PCOS patients exhibit more severe insulin resistance than the general population independent of obesity status, indicating that metabolic abnormalities in PCOS cannot be simply attributed to excess body weight [6]. Moreover, the severity of IR is positively correlated with body fat mass and further disturbs hormonal homeostasis in affected women.

Adipose tissue is now regarded as a functional endocrine organ that secretes a variety of adipokines to regulate energy balance and hormonal metabolism. Mounting studies have confirmed that adipokines participate in the pathogenesis of PCOS and are closely correlated with IR and hyperandrogenism [7]. Aberrant expression of chemerin, visfatin and other adipokines has been frequently observed in PCOS patients. These adipokines may contribute to disease progression by modulating inflammatory responses and insulin sensitivity [8-10]. PCOS is also closely linked to chronic inflammation and immune dysfunction, which partially explains the increased long-term cardiovascular risk in this population. Additionally, abnormal neuroendocrine regulation is involved in PCOS pathogenesis. Anti-Müllerian hormone and related neuropeptides could modulate the luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio and thus influence the disease progression [11].

Current clinical management of PCOS primarily targets metabolic derangements and endocrine dysfunction. Lifestyle intervention and weight loss are first-line strategies, which can effectively improve IR, hyperandrogenism and menstrual irregularities [12]. Insulin sensitizers such as metformin have been demonstrated to ameliorate body mass, IR and androgen levels in PCOS patients [13]. In recent years, glucagon-like peptide-1 receptor agonists (GLP-1RAs), a novel class of glucose-lowering agents, have been increasingly applied in PCOS management. GLP-1RAs exert beneficial effects on weight reduction, metabolic profiles and hyperandrogenism [14]. Nevertheless, the exact role of chemerin and visfatin in PCOS pathogenesis, as well as their correlations with IR and hormonal alterations, are not fully elucidated.

Materials and methods

Study design

A total of 338 obese women with PCOS admitted to Qingyang People's Hospital between January 2019 and December 2023 were enrolled in this retrospective study. According to the treatment regimen, patients were divided into a control group (n=168, pioglitazone alone) and a combination group (n=170, pioglitazone combined with liraglutide). The treatment course lasted 24 weeks in both groups. The study protocol was approved by the Ethics Committee of Qingyang People's Hospital and conducted in strict accordance with the principles of the Declaration of Helsinki.

Sample size was calculated using the single population proportion formula: $N = Z^2 \times [P \times (1-P)]/E^2$. Based on previous literature, the overall clinical response rate of PCOS treatment was assumed to be 86.49% [15]. With α=0.05 (Z=1.96) and an allowable error of 0.05, the minimal required sample size was 180. After accounting for a 10% dropout and missing data rate, approximately 200 participants were needed. The final enrolled sample of 338 cases adequately met this requirement.

Clinical data collection

PCOS was diagnosed according to the Rotterdam diagnostic criteria [15]. All patients were required to meet at least two of the following three items: oligovulation or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on pelvic ultrasound, with other related endocrine disorders excluded.

Inclusion criteria: confirmed diagnosis of PCOS; body mass index (BMI) ≥28 kg/m^2; age 18-40 years; completion of the full 24-week treatment course; and complete clinical and laboratory data.

Exclusion criteria: thyroid dysfunction, hyperprolactinemia, Cushing's syndrome, congenital adrenal hyperplasia, type 2 diabetes mellitus, severe hepatic or renal insufficiency, malignant

tumors; use of any medications affecting glucose and lipid metabolism or sex hormone levels within the preceding 3 months; pregnancy or lactation; and incomplete clinical data.

Data collection

Baseline demographic indicators included age and disease duration. Clinical and laboratory parameters recorded at baseline and post-treatment comprised BMI, waist circumference, fasting plasma glucose (FPG), fasting insulin (FINS), homeostasis model assessment of IR (HOMA-IR), triglycerides (TG), and testosterone (T). Serum chemerin and visfatin levels as well as the chemerin/visfatin ratio were also detected. Adverse events during treatment were recorded throughout the follow-up period.

Treatment methods

In the control group, pioglitazone was administered once daily with dosage individualized according to baseline HOMA-IR: 30 mg/day for patients with HOMA-IR ≥4.5, and 15 mg/day for those with HOMA-IR <4.5 [16, 17]. The combination group received the same pioglitazone regimen plus liraglutide. Liraglutide was initiated at 0.6 mg/day in the first two weeks, increased to 1.2 mg/day during weeks 3-4, and further increased to a maintenance dose of 1.8 mg/day from week 5 onward if well tolerated. Patients intolerant to 1.8 mg/day remained on 1.2 mg/day as a maintenance dose [18, 19]. The treatment duration was 24 weeks in both groups.

Measurement methods

Fasting venous blood samples were collected in the early morning at baseline and after 24 weeks of treatment. Biochemical indicators including FPG and TG were detected using an automatic biochemical analyzer (Hitachi 7600, Hitachi, Japan). FINS and sex hormones were measured by chemiluminescence immunoassay on a Roche Cobas e601 analyzer (Roche Diagnostics).

Serum chemerin and visfatin concentrations were determined by commercial enzyme-linked immunosorbent assay (ELISA) kits. Chemerin was measured using the Elabscience Human Chemerin ELISA Kit (Cat. No. E-EL-H0698; detection range: 0.16-10 ng/mL; sensitivity: 0.1 ng/mL). Visfatin was assayed with the Elabscience Human Visfatin ELISA Kit (Cat. No. E-EL-H1763; detection range: 0.31-20 ng/mL; sensitivity: 0.19 ng/mL). All ELISA kits were purchased from Shanghai Enzyme-Linked Biotechnology Co., Ltd. All experimental procedures were performed strictly in accordance with the manufacturer's instructions. HOMA-IR was calculated using the formula: HOMA-IR = FPG × FINS/22.5.

Outcome measures

The primary outcome was the improvement of IR and changes in related metabolic biomarkers. ΔHOMA-IR was defined as the reduction in HOMA-IR from baseline to post-treatment, reflecting the magnitude of IR improvement; a higher ΔHOMA-IR indicated a better therapeutic effect. Using the median ΔHOMA-IR value of 1.97 as the cutoff, patients were classified into an improved group (ΔHOMA-IR ≥1.97) and a non-improved group (ΔHOMA-IR <1.97).

Secondary outcomes included changes in BMI, waist circumference, FPG, FINS, TG, T, chemerin, visfatin, and the chemerin/visfatin ratio. Clinical efficacy at 24 weeks was independently evaluated by two clinicians blinded to group allocation (inter-rater agreement: Cohen's κ=0.884; discrepancies were resolved by consensus) and categorized into three grades based on four evaluation dimensions. Markedly effective: HOMA-IR reduction ≥50% from baseline, BMI reduction ≥10%, regular menstrual cycles restored to 21-35 days for at least two consecutive cycles, and testosterone levels within the normal reference range. Effective: HOMA-IR reduction of 20-49%, BMI reduction of 5-9%, improved but incompletely normalized menstrual cyclicity, and decreased testosterone still above the upper normal limit. Ineffective: HOMA-IR reduction <20% or deterioration of indicators, with no remarkable improvement in BMI, menstrual regularity or testosterone level.

The total clinical response rate was defined as the proportion of patients achieving markedly effective or effective outcomes. Adverse events were documented during the treatment. Furthermore, we analyzed correlations between baseline parameters and HOMA-IR, correlations between dynamic biomarker changes and ΔHOMA-IR, and the predictive value of serum

chemerin, visfatin and their ratio for IR improvement.

Notably, the two outcome evaluation systems served different research purposes. Dichotomized IR improvement (ΔHOMA-IR ≥ median) was used as the dependent variable in logistic regression to screen independent predictive factors, given that HOMA-IR reflects the core pathophysiological characteristics of PCOS. The multidimensional clinical efficacy grading was used to comprehensively assess therapeutic effects covering hormonal and menstrual improvements. The two evaluation approaches were complementary and not designed for direct comparison.

Statistical analysis

All statistical analyses were performed with R 4.5.2 and SPSS 28.0. Normally distributed continuous data were presented as mean ± standard deviation; independent-sample t-test and paired t-test were used for between-group and within-group comparisons, respectively. Non-normally distributed data were expressed as median (interquartile range) and compared using the Mann-Whitney U test or Wilcoxon signed-rank test. Categorical variables were described as case number (percentage) and analyzed via the chi-square test or Fisher's exact test when appropriate.

Correlation analysis was conducted using Pearson or Spearman correlation according to the data distribution. Logistic regression was performed with IR improvement as the dependent variable (0 = non-improved, 1 = improved). Variables with P<0.10 in univariate analysis were included in the multivariate regression model. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Variance inflation factor (VIF) was used to assess multicollinearity, and VIF<5 was regarded as acceptable.

Receiver operating characteristic (ROC) curves were constructed to assess the predictive efficacy of chemerin, visfatin and the chemerin/visfatin ratio for IR improvement. The area under the curve (AUC), optimal cutoff value, sensitivity and specificity were calculated. The optimal cutoff point was determined according to the Youden index. A two-tailed *P* value <0.05 was considered statistically significant.

Results

Baseline characteristics

Age differed significantly between the combination group and the control group (P=0.017). No significant intergroup differences were observed in disease duration, age at menarche, menstrual cycle pattern, marital status, reproductive history, infertility history, educational level, type of menstrual abnormality, family history of diabetes, smoking history, or physical activity habits (all P>0.05; **Table 1**).

Changes in BMI and waist circumference

Before treatment, BMI and waist circumference were comparable between the two groups (P=0.900 and P=0.220, respectively). After treatment, both BMI and waist circumference were significantly lower in the combination group than those in the control group (both P<0.001). Within-group comparisons revealed significant reductions in these two anthropometric indicators after treatment in both groups (both P<0.001; **Figure 1**; Table S1).

Changes in glucose metabolism and IR

FPG, FINS, and HOMA-IR were similar at baseline between the two groups (P=0.597, P=0.745, P=0.837, respectively). Post-treatment levels of FPG, FINS and HOMA-IR were markedly lower in the combination group than those in the control group (all P<0.001). Both groups also presented significant within-group improvements in glucose metabolism and IR after intervention (all P<0.001; **Figure 2**; Table S1).

Changes in lipid metabolism and reproductive hormones

Baseline levels of total cholesterol (TC), triglycerides (TG), luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), and the LH/FSH ratio were balanced between the two groups (all P>0.05). After treatment, TC, TG, LH, T and LH/FSH ratio were significantly decreased in the combination group compared with the control group (all P<0.001), while FSH levels remained comparable (P=0.418). Within-group analysis showed significant reductions in TC, TG, LH, T and LH/FSH ratio in both groups after treatment (all P<

Table 1. Comparison of baseline characteristics between the two groups

Variable	Combination group (n=170)	Control group (n=168)	Statistic	*P* value
Age (years)	29.02 ± 5.01	27.83 ± 4.07	2.397	0.017
Disease duration (years)	3.00 (2.00, 4.00)	3.00 (3.00, 4.00)	13721.5	0.524
Age at menarche (years)	13.00 (12.00, 14.00)	13.00 (12.00, 14.00)	14449	0.848
Menstrual cycle (days)	82.92 ± 25.62	82.01 ± 26.74	0.322	0.748
Marital status			0.284	0.594
Married	102 (60.00%)	96 (57.14%)		
Unmarried	68 (40.00%)	72 (42.86%)		
Childbearing history			0.357	0.55
Yes	64 (37.65%)	58 (34.52%)		
No	106 (62.35%)	110 (65.48%)		
History of infertility			0.562	0.453
Yes	56 (32.94%)	49 (29.17%)		
No	114 (67.06%)	119 (70.83%)		
Educational level			0.93	0.628
Junior high school or below	31 (18.24%)	35 (20.83%)		
High school/technical secondary school	71 (41.76%)	74 (44.05%)		
College degree or above	68 (40.00%)	59 (35.12%)		
Type of menstrual abnormality			0.617	0.734
Oligomenorrhea	94 (55.29%)	98 (58.33%)		
Amenorrhea	50 (29.41%)	43 (25.60%)		
Irregular uterine bleeding	26 (15.29%)	27 (16.07%)		
Family history of diabetes			0.461	0.497
Yes	47 (27.65%)	41 (24.40%)		
No	123 (72.35%)	127 (75.60%)		
Smoking history			0.325	0.569
Yes	15 (8.82%)	12 (7.14%)		
No	155 (91.18%)	156 (92.86%)		
Regular exercise habit			0.422	0.516
Yes	52 (30.59%)	46 (27.38%)		
No	118 (69.41%)	122 (72.62%)		

Note: PCOS: Polycystic Ovary Syndrome, BMI: Body Mass Index.

0.001). FSH levels did not change obviously in either group (both P>0.05; **Figure 3**; Table S1).

Changes in serum chemerin, visfatin, and the chemerin/visfatin ratio

Baseline serum chemerin, visfatin and chemerin/visfatin ratio were similar between the two groups (all P>0.05). After treatment, serum chemerin, visfatin and their ratio were all significantly lower in the combination group than those in the control group (all P<0.001). Both adipokines decreased significantly within each group after treatment (all P<0.001). The chemerin/visfatin ratio also decreased significantly in both groups (control group P=0.005; combination group P<0.001; **Figure 4**; Table S1).

Correlation between baseline HOMA-IR and related variables

Baseline HOMA-IR was positively correlated with BMI (r=0.443, P<0.001), waist circumference (r=0.484, P<0.001), chemerin (r=0.569, P<0.001), visfatin (r=0.360, P<0.001), chemerin/visfatin ratio (r=0.580, P<0.001), TG (r=0.373, P<0.001), and T (r=0.369, P<0.001; **Figure 5**).

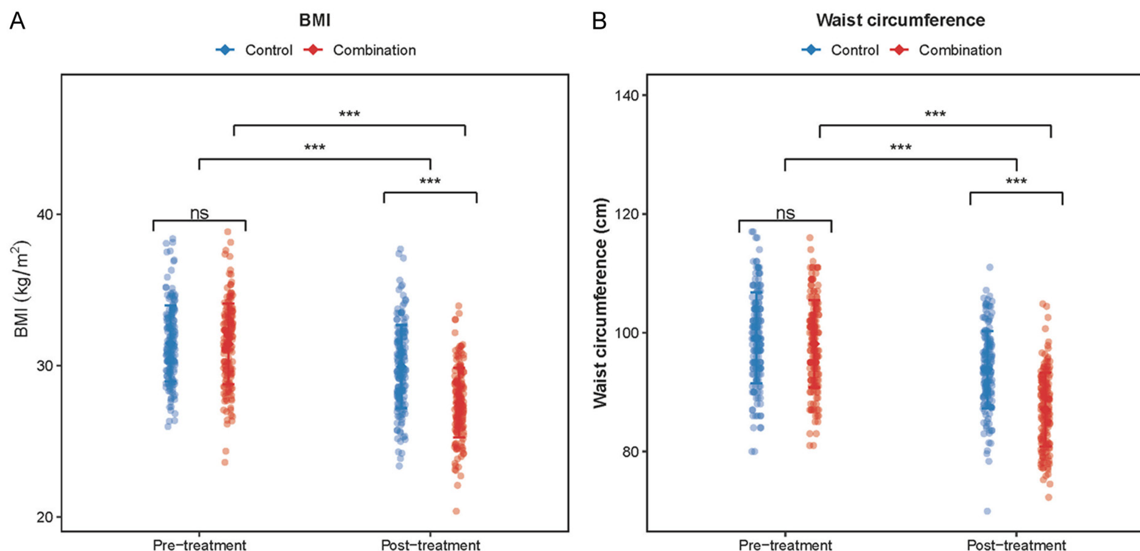

Figure 1. Comparison of changes in BMI and waist circumference before and after treatment in the two groups. A: Comparison of BMI changes before and after treatment in the two groups. B: Comparison of waist circumference changes before and after treatment in the two groups. Note: BMI: Body Mass Index. ***P<0.001, ns indicates no statistical significance.

Correlation between ΔHOMA-IR and dynamic changes in related variables

ΔHOMA-IR was positively correlated with Δ chemerin (r=0.475, P<0.001), Δvisfatin (r= 0.255, P<0.001), Δchemerin/visfatin ratio (r= 0.480, P<0.001), ΔBMI (r=0.355, P<0.001), and Δwaist circumference (r=0.343, P<0.001; **Figure 6**).

Predictive value of baseline chemerin, visfatin, and the chemerin/visfatin ratio

ROC curve analysis was performed with ΔHOMA-IR as the outcome variable. ΔHOMA-IR was defined as baseline HOMA-IR minus post-treatment HOMA-IR and dichotomized according to its median value. Participants with ΔHOMA-IR ≥1.97 were defined as having improved IR (coded as 1), and those with ΔHOMA-IR <1.97 were categorized into the non-improvement group (coded as 0).

Baseline chemerin, visfatin and chemerin/visfatin ratio all exhibited predictive efficacy for IR improvement, with AUC values of 0.670, 0.569 and 0.703, respectively. The chemerin/visfatin ratio yielded the best predictive performance, followed by chemerin, while visfatin showed relatively lower discriminatory ability. All three biomarkers possessed statistically significant predictive value (chemerin P<0.001, visfatin P=0.027, chemerin/visfatin ratio P< 0.001; **Figure 7**).

Logistic regression analysis of factors associated with IR improvement

With dichotomized ΔHOMA-IR as the dependent variable, univariate logistic regression revealed that treatment regimen, baseline chemerin/visfatin ratio, baseline BMI, baseline TG and baseline T were significantly associated with IR improvement (all P<0.001). By contrast, age, disease duration, baseline FPG and baseline FINS showed no significant association (all P>0.05, respectively).

Variables with P<0.10 in univariate analysis were included in the multivariate logistic regression model. The results demonstrated that treatment group (OR=4.858, 95% CI: 2.839-8.313, P<0.001), baseline chemerin/visfatin ratio (OR=1.281, 95% CI: 1.162-1.412, P<0.001), baseline BMI (OR=1.169, 95% CI: 1.054-1.297, P=0.003), baseline TG (OR= 1.874, 95% CI: 1.107-3.174, P=0.019), and baseline T (OR=2.997, 95% CI: 1.722-5.218, P<0.001) were independent influencing factors for IR improvement.

Collinearity diagnostics indicated no obvious multicollinearity among the enrolled variables. The VIFs for treatment group, chemerin/visfa-

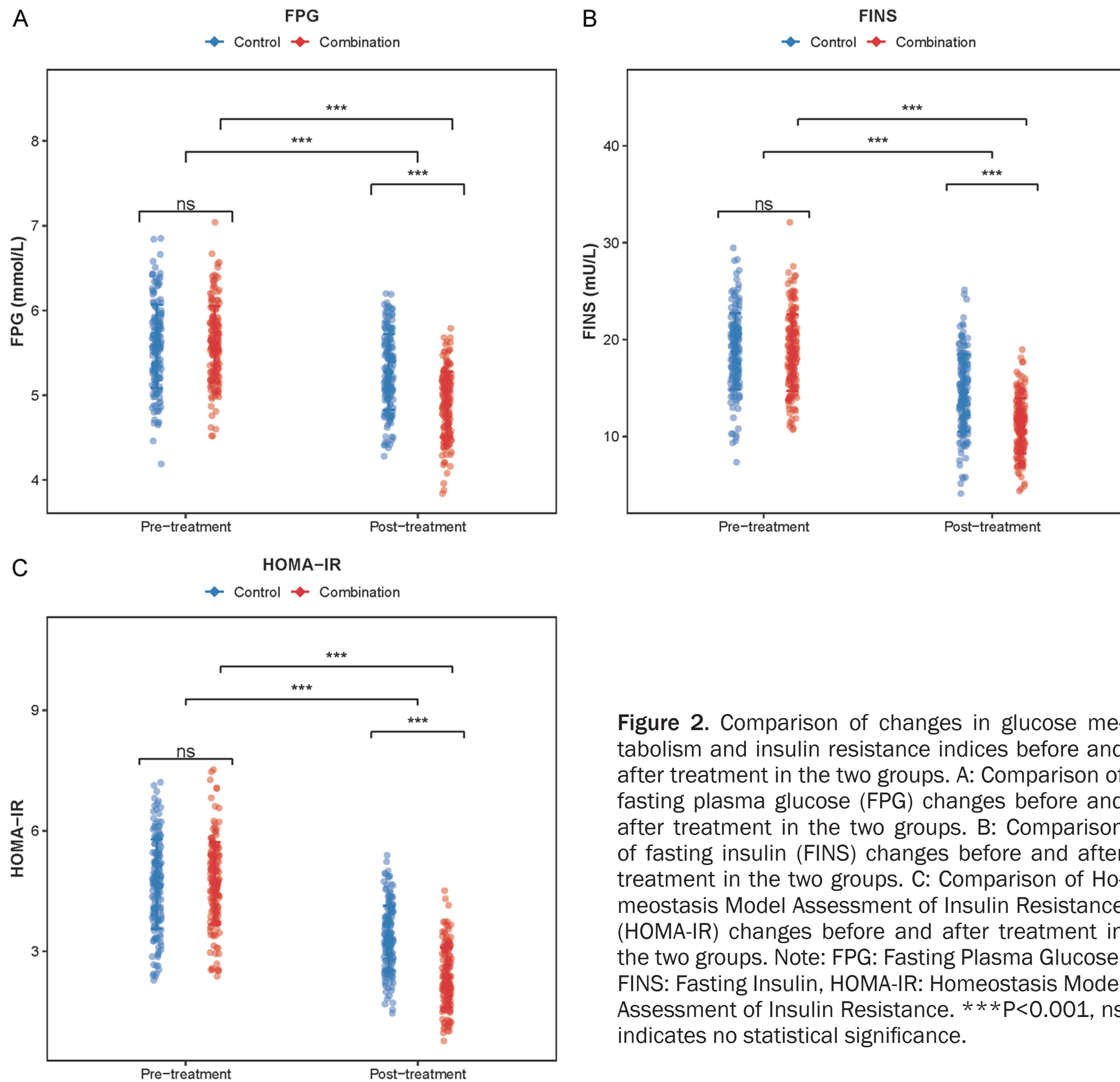

Figure 2. Comparison of changes in glucose metabolism and insulin resistance indices before and after treatment in the two groups. A: Comparison of fasting plasma glucose (FPG) changes before and after treatment in the two groups. B: Comparison of fasting insulin (FINS) changes before and after treatment in the two groups. C: Comparison of Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) changes before and after treatment in the two groups. Note: FPG: Fasting Plasma Glucose, FINS: Fasting Insulin, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance. ***P<0.001, ns indicates no statistical significance.

tin ratio, BMI, TG and T were 1.123, 1.056, 1.022, 1.057 and 1.038, respectively, all lower than 5, confirming no significant multicollinearity. The multivariate model had an AUC of 0.812, indicating good discriminatory power (**Figure 8**).

Interaction analysis

To explore potential interactive effects, two interaction models were constructed: treatment group with baseline chemerin/visfatin ratio and treatment group with baseline BMI. The interaction between treatment group and chemerin/visfatin ratio was not statistically significant (P=0.468), and likewise, no significant interaction was found between treatment group and baseline BMI (P=0.512). These results indicated that baseline chemerin/visfatin ratio and BMI did not modify the therapeutic effect of combined therapy on IR improvement.

Notably, the main effect of treatment group became non-significant after introducing the interaction term into the model, accompanied by markedly widened confidence intervals. This is a recognized statistical phenomenon: when an interaction term is included, the main effect of the grouping variable is interpreted as its conditional effect when the continuous interacting variable equals zero, which is physiologically implausible for both BMI and chemerin/visfatin ratio. Therefore, the corresponding main effect coefficients cannot represent the overall therapeutic effect, and the primary multivariate model without interaction terms re-

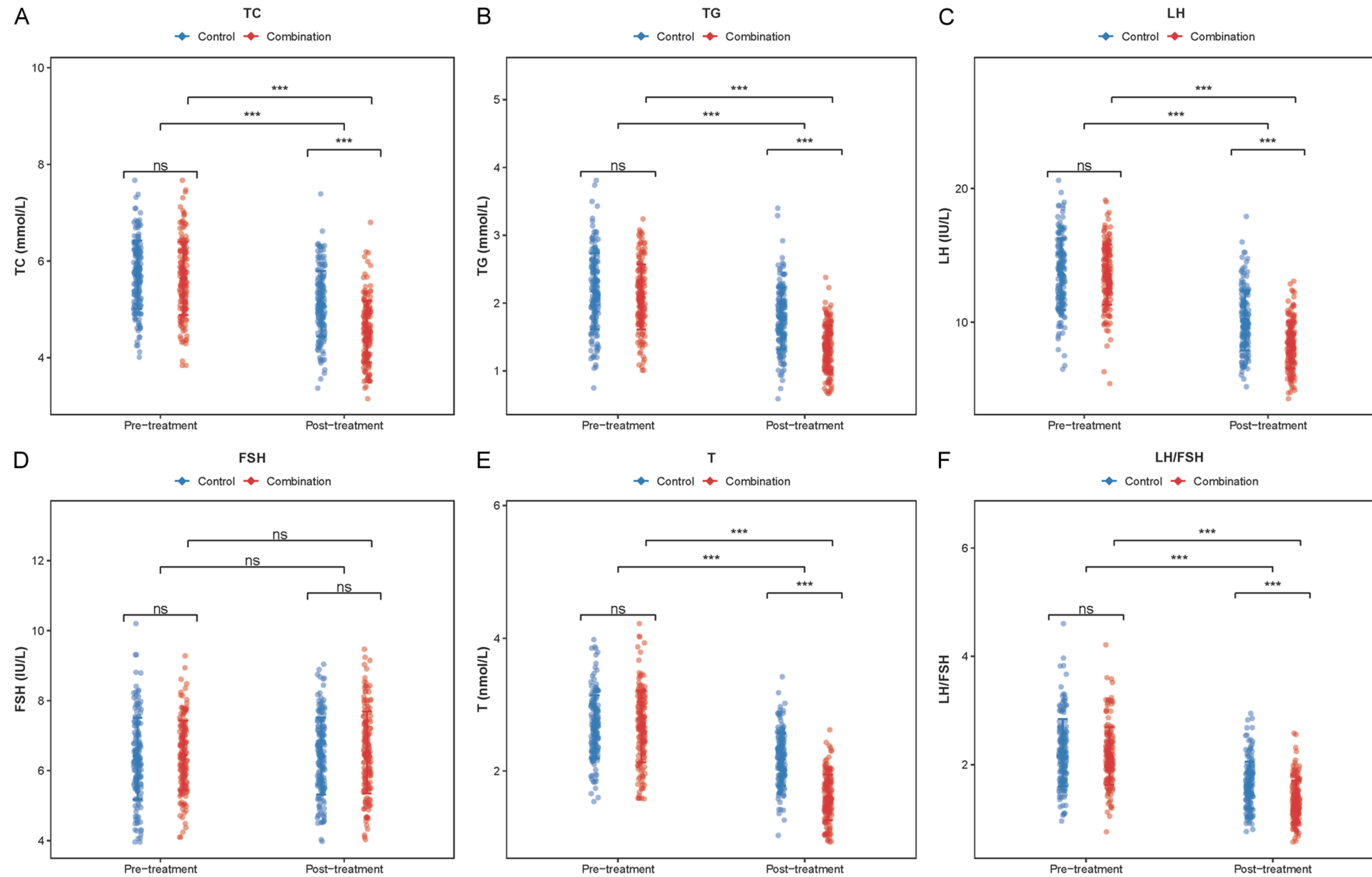

Figure 3. Comparison of changes in lipid metabolism and reproductive hormone indices before and after treatment in the two groups. A: Comparison of total cholesterol (TC) changes before and after treatment in the two groups. B: Comparison of triglyceride (TG) changes before and after treatment in the two groups. C: Comparison of luteinizing hormone (LH) changes before and after treatment in the two groups. D: Comparison of follicle-stimulating hormone (FSH) changes before and after treatment in the two groups. E: Comparison of testosterone (T) changes before and after treatment in the two groups. F: Comparison of LH/FSH changes before and after treatment in the two groups. Note: TC: Total Cholesterol, TG: Triglycerides, LH: Luteinizing Hormone, FSH: Follicle-Stimulating Hormone, T: Testosterone. ***P<0.001, ns indicates no statistical significance.

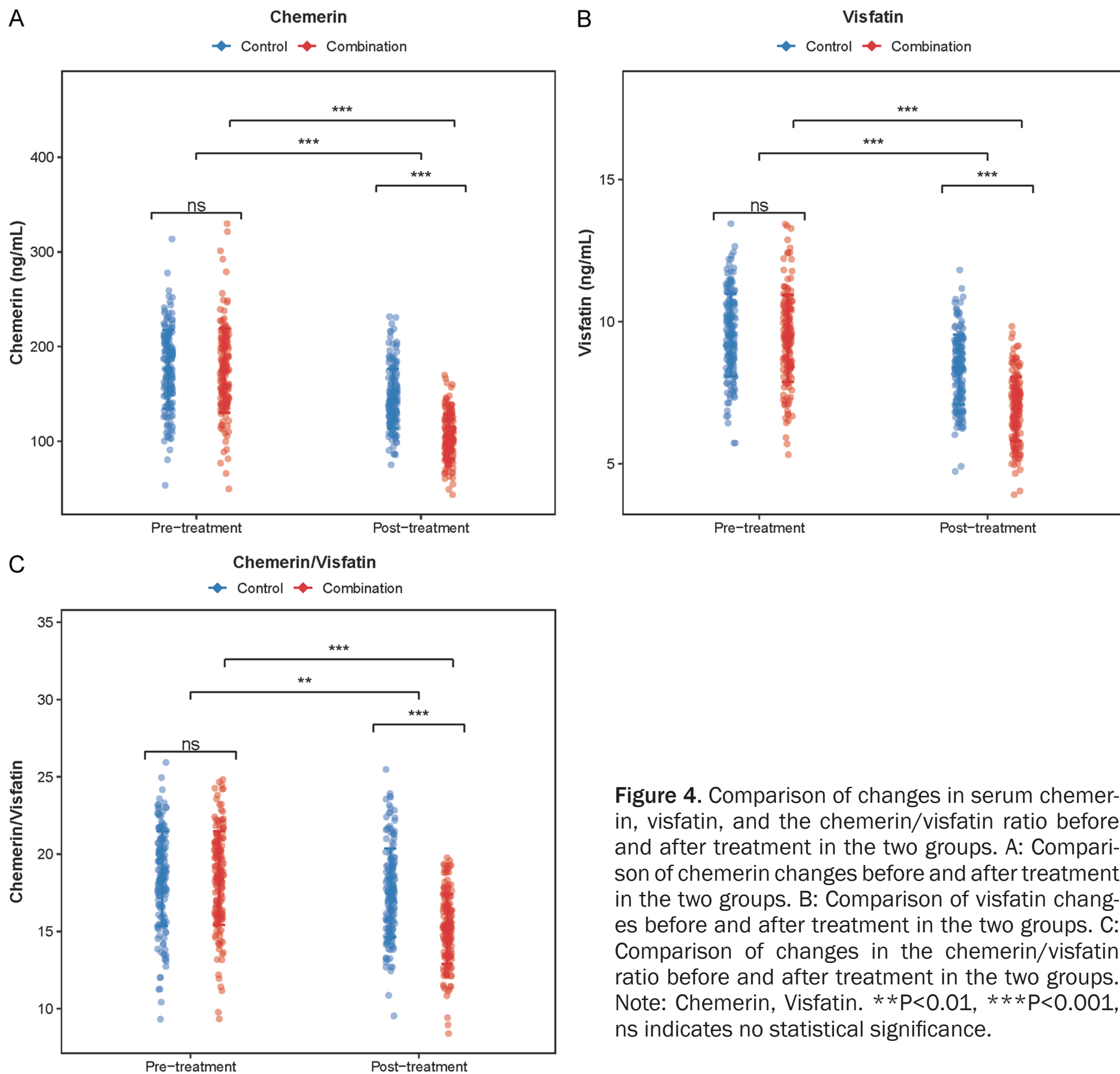

Figure 4. Comparison of changes in serum chemerin, visfatin, and the chemerin/visfatin ratio before and after treatment in the two groups. A: Comparison of chemerin changes before and after treatment in the two groups. B: Comparison of visfatin changes before and after treatment in the two groups. C: Comparison of changes in the chemerin/visfatin ratio before and after treatment in the two groups. Note: Chemerin, Visfatin. **P<0.01, ***P<0.001, ns indicates no statistical significance.

mains appropriate for evaluating the overall treatment effect (OR=4.858, 95% CI: 2.839-8.313, P<0.001).

In Model 1, baseline chemerin/visfatin ratio (P<0.001), baseline BMI (P=0.003), baseline TG (P=0.022) and baseline T (P<0.001) remained significantly correlated with IR improvement, whereas the main effect of treatment group was insignificant (P=0.122). In Model 2, baseline chemerin/visfatin ratio (P<0.001), baseline TG (P=0.020) and baseline T (P<0.001) maintained statistical significance, while treatment group (P=0.852) and baseline BMI (P=0.084) did not. Interaction visualization showed that the predicted probability of IR improvement increased along with elevated baseline chemerin/visfatin ratio and BMI, yet the trend curves of the two treatment groups remained nearly parallel, further verifying the absence of a meaningful interaction (**Tables 2**, S2, S3; **Figure 9**).

Clinical efficacy

The combination group achieved superior clinical efficacy compared with the control group. In the combination group, 101 patients (59.41%) were rated as markedly effective, 56 (32.94%) as effective, and 13 (7.65%) as ineffective. In the control group, 78 patients (46.43%) were markedly effective, 54 (32.14%) effective, and 36 (21.43%) ineffective. The distribution of efficacy grades differed significantly between the two groups (χ^2=13.776, P=0.001). The overall clinical response rate was 92.35% in the com-

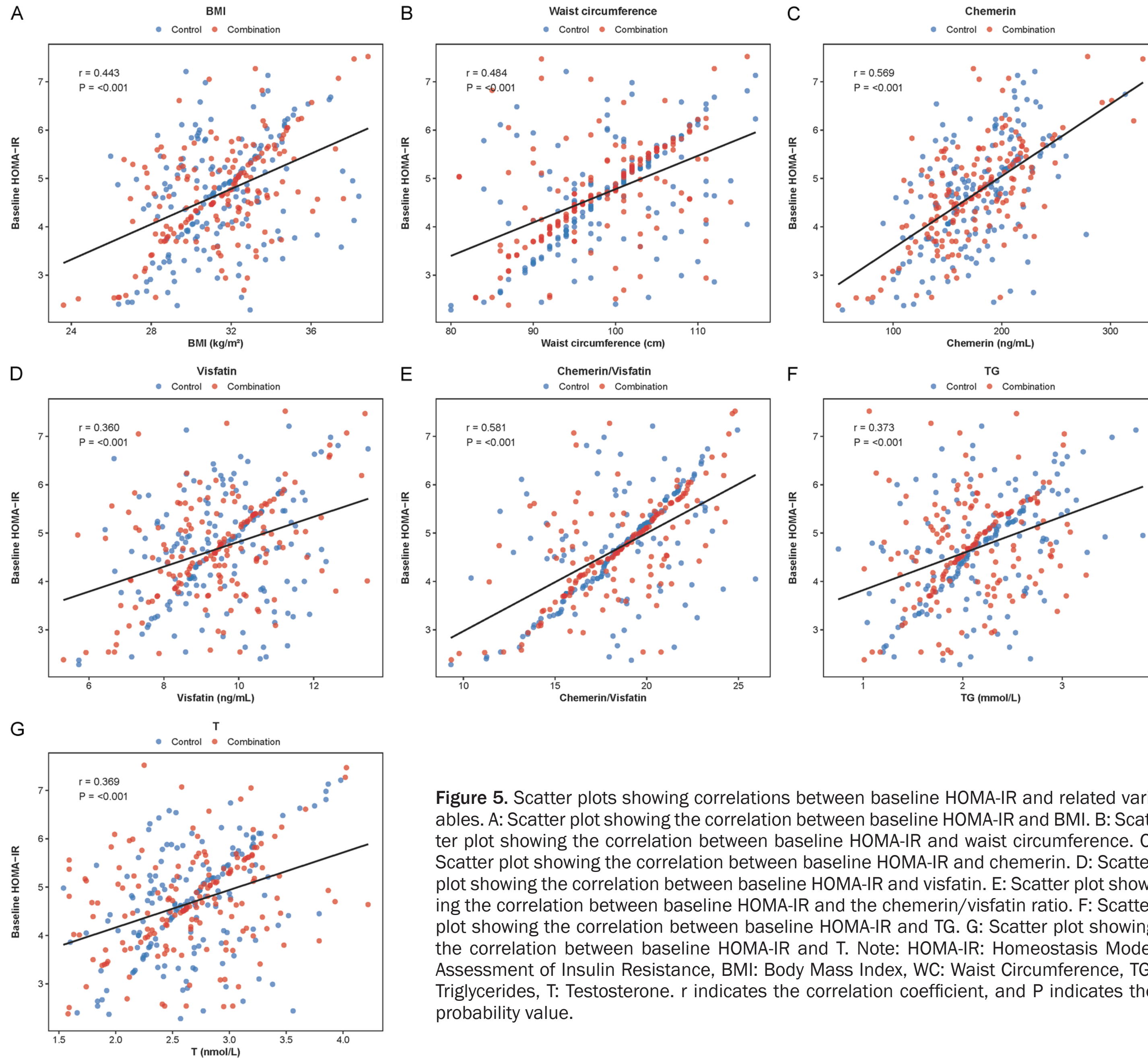

Figure 5. Scatter plots showing correlations between baseline HOMA-IR and related variables. A: Scatter plot showing the correlation between baseline HOMA-IR and BMI. B: Scatter plot showing the correlation between baseline HOMA-IR and waist circumference. C: Scatter plot showing the correlation between baseline HOMA-IR and chemerin. D: Scatter plot showing the correlation between baseline HOMA-IR and visfatin. E: Scatter plot showing the correlation between baseline HOMA-IR and the chemerin/visfatin ratio. F: Scatter plot showing the correlation between baseline HOMA-IR and TG. G: Scatter plot showing the correlation between baseline HOMA-IR and T. Note: HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, BMI: Body Mass Index, WC: Waist Circumference, TG: Triglycerides, T: Testosterone. r indicates the correlation coefficient, and P indicates the probability value.

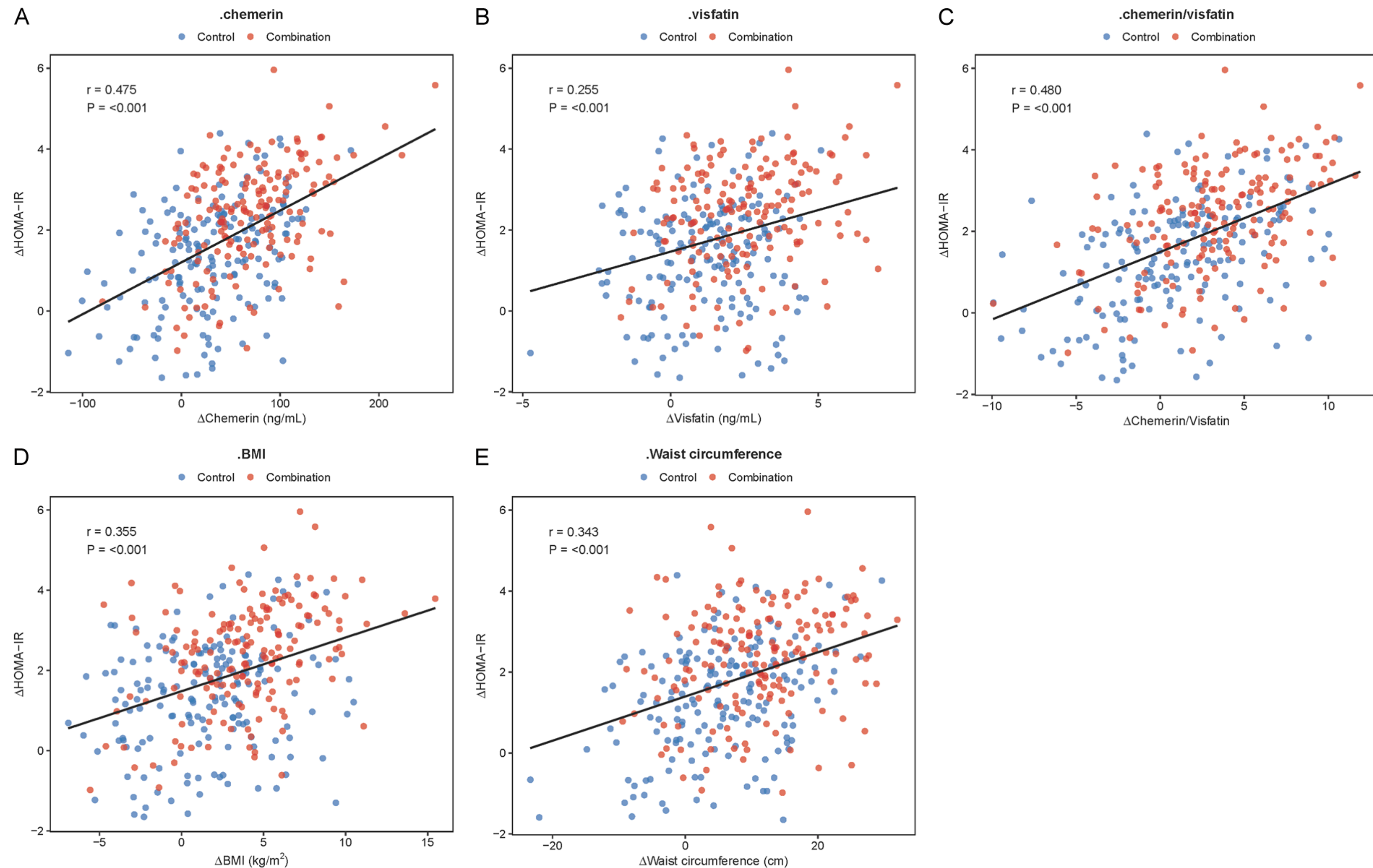

Figure 6. Scatter plots showing correlations between ΔHOMA-IR and changes in related variables. A: Scatter plot showing the correlation between ΔHOMA-IR and Δchemerin. B: Scatter plot showing the correlation between ΔHOMA-IR and Δvisfatin. C: Scatter plot showing the correlation between ΔHOMA-IR and the Δchemerin/visfatin ratio. D: Scatter plot showing the correlation between ΔHOMA-IR and ΔBMI. E: Scatter plot showing the correlation between ΔHOMA-IR and Δwaist circumference. Note: HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, BMI: Body Mass Index, WC: Waist Circumference, Chemerin, Visfatin. Δ indicates pre-treatment minus post-treatment, with a larger Δ indicating greater improvement; r indicates the correlation coefficient; P indicates the probability value.

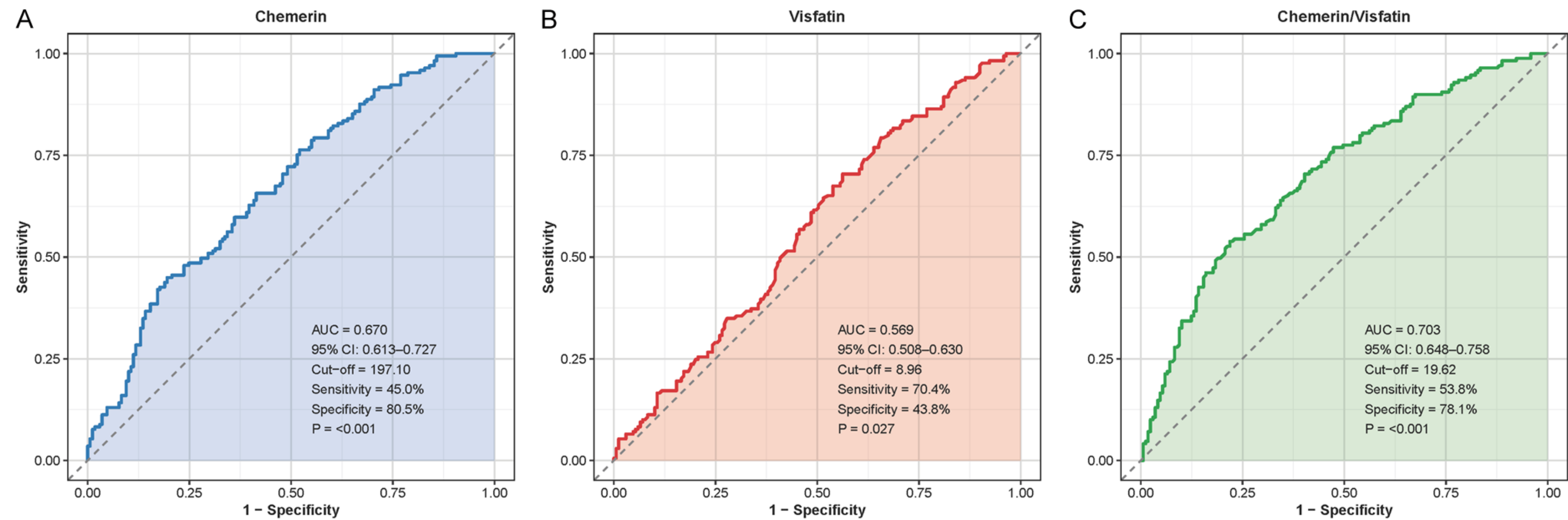

Figure 7. Receiver operating characteristic (ROC) curves of baseline chemerin, visfatin, and the chemerin/visfatin ratio for predicting improvement in insulin resistance. A: ROC curve of baseline chemerin for predicting improvement in insulin resistance. B: ROC curve of baseline visfatin for predicting improvement in insulin resistance. C: ROC curve of the baseline chemerin/visfatin ratio for predicting improvement in insulin resistance. Note: ROC: Receiver Operating Characteristic, AUC: Area Under the Curve, CI: Confidence Interval, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance. ΔHOMA-IR was defined as pre-treatment HOMA-IR minus post-treatment HOMA-IR. Improvement was coded as 1 when ΔHOMA-IR was greater than or equal to the median value and as 0 otherwise. Cut-off indicates the optimal threshold determined by the Youden index, sensitivity indicates the true positive rate, and specificity indicates the true negative rate.

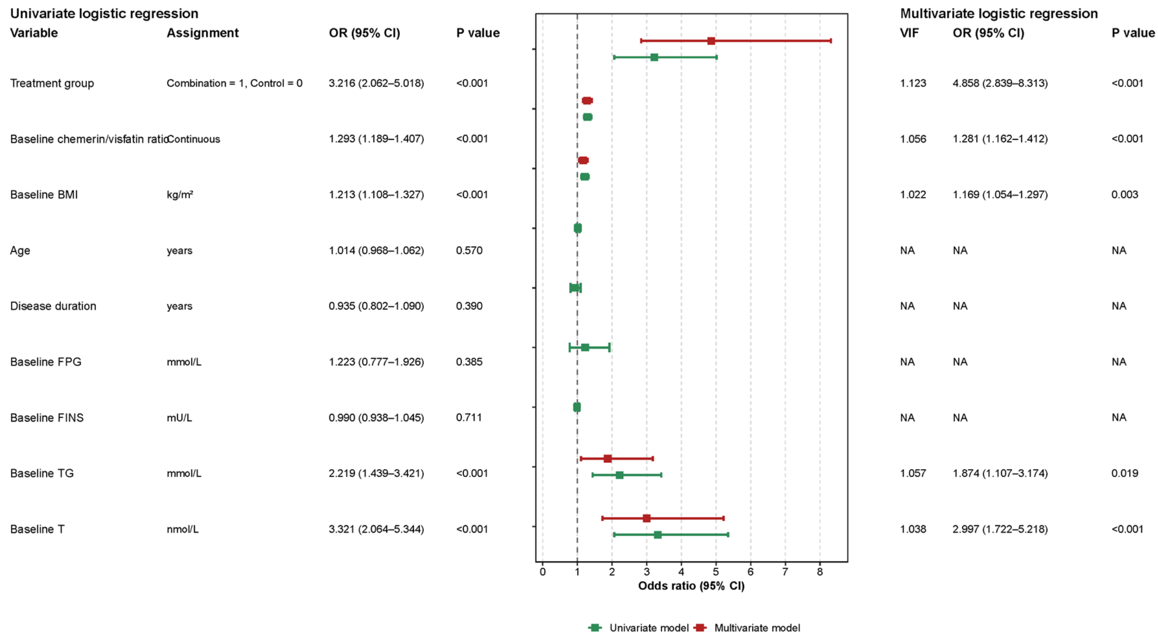

Figure 8. Forest plot of logistic regression analysis of factors associated with improvement in insulin resistance. Note: HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, VIF: Variance Inflation Factor, OR: Odds Ratio, CI: Confidence Interval, FPG: Fasting Plasma Glucose, FINS: Fasting Insulin, TG: Triglycerides, T: Testosterone, BMI: Body Mass Index. ΔHOMA-IR was defined as pre-treatment HOMA-IR minus post-treatment HOMA-IR. Improvement in insulin resistance was coded as 1 when ΔHOMA-IR was greater than or equal to the median value and as 0 otherwise. Univariate indicates univariate logistic regression, and multivariate indicates multivariate logistic regression.

Table 2. Interaction analysis of treatment group with baseline chemerin/visfatin ratio and baseline BMI for improvement in insulin resistance

Interaction model	Interaction term	β	SE	OR (95% CI)	*P* value
Model 1	Treatment × baseline chemerin/visfatin ratio	-0.073	0.101	0.930 (0.761-1.131)	0.468
Model 2	Treatment × baseline BMI	0.07	0.107	1.073 (0.870-1.328)	0.512

Note: HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, BMI: Body Mass Index, TG: Triglycerides, T: Testosterone, SE: Standard Error, OR: Odds Ratio, CI: Confidence Interval.

bination group and 78.57% in the control group, with a significant intergroup difference (χ^2=12.947, P<0.001; **Table 3**).

Adverse reactions

The incidence rates of nausea/vomiting, abdominal distension/diarrhea, dizziness/fatigue and mild edema were all comparable between the two groups (all P>0.05). The overall incidence of adverse events was 11.76% in the combination group and 10.12% in the control group, with no significant difference (χ^2=0.235, P=0.628). These findings suggested that liraglutide combined with pioglitazone did not increase the risk of adverse reactions (**Table 4**).

Discussion

This retrospective study of 338 women with obese PCOS evaluated the efficacy and safety of liraglutide combined with pioglitazone, and examined changes in metabolic parameters and adipokine profiles. We also explored factors associated with IR improvement and assessed potential predictive biomarkers. Compared with pioglitazone monotherapy, the combination regimen resulted in significantly greater reductions in BMI, waist circumference, fasting plasma glucose, fasting insulin, and HOMA-IR. Serum levels of chemerin, visfatin, their ratio, and reproductive hormone profiles also improved more markedly in the combination group. The dual-treatment group achieved

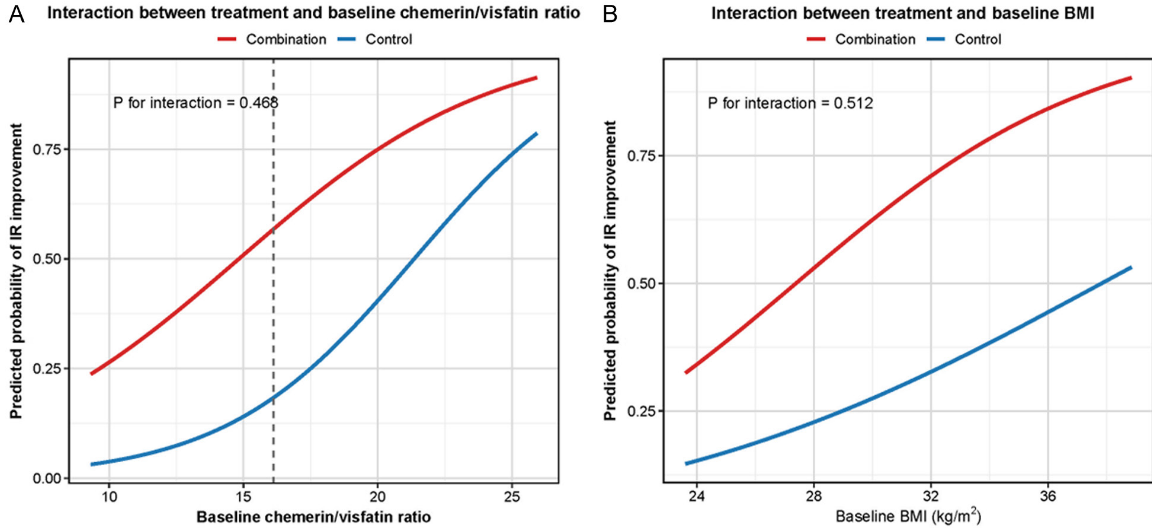

Figure 9. Interaction plots of the treatment group with baseline chemerin/visfatin ratio and baseline BMI for improvement in insulin resistance. A: Interaction plot of treatment group and baseline chemerin/visfatin ratio for the predicted probability of improvement in insulin resistance. B: Interaction plot of treatment group and baseline BMI for the predicted probability of improvement in insulin resistance. Note: HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, BMI: Body Mass Index, TG: Triglycerides, T: Testosterone. Improvement in insulin resistance was defined according to the binary coding based on ΔHOMA-IR. P for interaction indicates the significance of the interaction term between treatment and the corresponding baseline variable.

Table 3. Comparison of clinical efficacy between the control group and the combination group

Outcome	Control (n=168)	Combination (n=170)	χ^2	*P* value
Markedly effective	78 (46.43%)	101 (59.41%)		
Effective	54 (32.14%)	56 (32.94%)		
Ineffective	36 (21.43%)	13 (7.65%)	13.776	0.001
Total effective rate	132 (78.57%)	157 (92.35%)	12.947	<0.001

Table 4. Comparison of adverse events between the control group and the combination group

Adverse event	Control (n=168)	Combination (n=170)	Test statistic	*P* value
Nausea/vomiting	5 (2.98%)	8 (4.71%)	0.684	0.408
Abdominal distension/diarrhea	4 (2.38%)	6 (3.53%)	-	0.75
Dizziness/fatigue	3 (1.79%)	3 (1.76%)	-	1
Mild edema	5 (2.98%)	3 (1.76%)	-	0.501
Any adverse event	17 (10.12%)	20 (11.76%)	0.235	0.628

a significantly higher overall clinical response rate, without an increase in adverse events. Consistent with previous reports, weight loss and metabolic intervention effectively improved HOMA-IR and hyperandrogenism in women with PCOS [12]. In a study by Elkind-Hirsch et al. [14], liraglutide reduced body weight and improved endocrine markers. Other studies have also confirmed the beneficial effects of GLP-1 receptor agonists on BMI, waist circumference, and multiple metabolic parameters [3, 20].

Women with obese PCOS frequently present with severe IR, which is not merely a metabolic feature but a core component of the pathogenic process. IR may exacerbate hyperandrogenism by stimulating androgen production in ovarian stromal cells and reducing sex hormone-binding globulin synthesis, creating a self-perpetuating pathological cycle [21, 22]. Therefore, improving IR represents a key therapeutic target in PCOS. In the present study, combination treatment was more effective in reducing

HOMA-IR than monotherapy, accompanied by more pronounced reductions in BMI and waist circumference. This indicates that liraglutide with pioglitazone may enhance insulin sensitivity through complementary mechanisms. Pioglitazone, a peroxisome proliferator-activated receptor γ (PPAR-γ) agonist, promotes adipocyte differentiation and enhances peripheral insulin sensitivity. Liraglutide, a GLP-1 receptor agonist, controls body weight by delaying gastric emptying and suppressing appetite, and has been approved for the management of type 2 diabetes [11, 23-25]. The two agents act synergistically, achieving weight reduction while improving insulin sensitivity.

Combination treatment also exerted superior effects on lipid metabolism and reproductive endocrine function. Hyperandrogenism and dyslipidemia commonly coexist in PCOS, and IR is closely involved in both conditions. Dysregulated insulin signaling disrupts lipid metabolism and steroidogenesis through multiple pathways. Hyperinsulinemia increases ovarian androgen production and reduces sex hormone-binding globulin levels, thereby exacerbating hyperandrogenism [26, 27]. In our study, TG, T, and the LH/FSH ratio decreased significantly after combination treatment, indicating that improved insulin sensitivity was accompanied by alleviated metabolic and endocrine disturbances. Zhang et al. [6] also reported that women with PCOS, regardless of obesity status, exhibit more severe IR and hormonal abnormalities. In the present study, FSH levels remained unchanged, suggesting that FSH is less sensitive to insulin resistance per se and is more strongly regulated by the hypothalamic-pituitary-ovarian axis. As reported by Pratama et al. [11], the LH/FSH ratio is modulated by multiple neuroendocrine factors rather than by metabolic status alone.

The roles of adipokines in PCOS have gained increasing attention. Chemerin and visfatin are adipose tissue-derived cytokines that participate in inflammatory responses, lipid metabolism, and glucose homeostasis [28, 29]. In our study, serum chemerin, visfatin, and the chemerin/visfatin ratio decreased significantly in both groups after treatment, indicating that these adipokines are closely associated with metabolic improvement. Previous studies have demonstrated that adipokine-mediated changes in insulin sensitivity and inflammatory activity contribute to the pathogenesis of PCOS [7]. Inflammation and immune dysregulation also play important roles in the metabolic disturbances observed in PCOS [10], which finding is further supported by our findings. Baseline HOMA-IR was positively correlated with chemerin, visfatin, and their ratio, supporting that these adipokines are reflective of insulin resistance. We further explored the correlations of ΔHOMA-IR with chemerin, visfatin and their ratio. Dynamic changes in these parameters were positively correlated with ΔHOMA-IR. In other words, elevated levels of chemerin, visfatin and their ratio were accompanied by an increase in ΔHOMA-IR, suggesting a progressive deterioration of insulin resistance over time in this population. Importantly, ROC curve analysis showed that the chemerin/visfatin ratio had a larger AUC than either marker alone, suggesting that this ratio provides more stable and reliable predictive performance in complex metabolic states [12].

Multivariable logistic regression revealed that treatment group, baseline chemerin/visfatin ratio, BMI, TG and T were independent factors associated with IR improvement. These findings indicate that treatment response depends not only on the therapeutic regimen but also on baseline metabolic and endocrine status. The chemerin/visfatin ratio remained significant in the multivariable model, supporting its potential value as a predictive biomarker. Previous studies have reported that body fat and metabolic status strongly influence changes in insulin sensitivity in women with PCOS [6]. All VIFs were below 5, indicating no significant multicollinearity and good model stability. The model AUC of 0.812 indicated strong discriminative performance, supporting its potential clinical utility for risk assessment and treatment prediction.

We further evaluated whether the treatment effect was modified by baseline chemerin/visfatin ratio or BMI. Neither interaction was statistically significant, indicating that the beneficial effect of combination treatment on IR was consistent across different baseline levels of these factors. In other words, the dual regimen improved IR regardless of baseline BMI or chemerin/visfatin ratio. These results are consistent with previous studies showing that GLP-

1 receptor agonists provide metabolic benefits across a range of body weight categories [20].

Safety outcomes were favorable. No significant between-group difference was observed in the incidence of adverse events, which were mostly mild gastrointestinal symptoms, dizziness, fatigue, or mild edema. No serious adverse events were reported. These findings indicate that combination therapy enhances efficacy without compromising tolerability, which is clinically meaningful. Previous studies have also reported that liraglutide-related adverse events are predominantly mild-to-moderate gastrointestinal reactions [14].

This study has several limitations. As a single-center retrospective study, it is susceptible to selection bias and information bias. In addition, biomarker measurements were obtained from routine clinical records rather than centralized research assays, so standardized intra- and inter-assay coefficients of variation could not be verified. This limitation is inherent to the retrospective design. The study population was relatively homogeneous, providing good internal validity but limited generalizability. The 24-week follow-up period did not allow assessment of long-term efficacy or recurrence. Dietary intake, physical activity, and treatment adherence were not strictly controlled, so complete adjustment for confounders was not possible. Further multicenter, prospective, randomized controlled trials with larger sample sizes are warranted to validate these findings.

Conclusion

In conclusion, liraglutide combined with pioglitazone significantly improves IR, body weight, glucose and lipid metabolism, and hyperandrogenism in women with obese PCOS, without increasing the risk of adverse events. Serum chemerin, visfatin, and the chemerin/visfatin ratio are closely correlated with IR and can serve as predictive biomarkers of treatment response. These adipokine markers may be useful for evaluating metabolic status and guiding personalized treatment strategies in obese PCOS.

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Disclosure of conflict of interest

None.

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References

[1] Helvaci N and Yildiz BO. Polycystic ovary syndrome as a metabolic disease. Nat Rev Endocrinol 2025; 21: 230-244.
[2] Chang KJ, Chen JH and Chen KH. The pathophysiological mechanism and clinical treatment of polycystic ovary syndrome: a molecular and cellular review of the literature. Int J Mol Sci 2024; 25: 9037.
[3] Bader S, Bhatti R, Mussa B and Abusanana S. A systematic review of GLP-1 on anthropometrics, metabolic and endocrine parameters in patients with PCOS. Womens Health (Lond) 2024; 20: 17455057241234530.
[4] Zhao H, Zhang J, Cheng X, Nie X and He B. Insulin resistance in polycystic ovary syndrome across various tissues: an updated review of pathogenesis, evaluation, and treatment. J Ovarian Res 2023; 16: 9.
[5] Bednarz K, Kowalczyk K, Cwynar M, Czapla D, Czarkowski W, Kmita D, Nowak A and Madej P. The role of Glp-1 receptor agonists in insulin resistance with concomitant obesity treatment in polycystic ovary syndrome. Int J Mol Sci 2022; 23: 4334.
[6] Zhang H, Wang W, Zhao J, Jiao P, Zeng L, Zhang H, Zhao Y, Shi L, Hu H, Luo L, Fukuzawa I, Li D, Li R and Qiao J. Relationship between body composition, insulin resistance, and hormonal profiles in women with polycystic ovary syndrome. Front Endocrinol (Lausanne) 2022; 13: 1085656.
[7] Xing C, Zhang J, Zhao H and He B. Effect of sex hormone-binding globulin on polycystic ovary syndrome: mechanisms, manifestations, genetics, and treatment. Int J Womens Health 2022; 14: 91-105.
[8] Wang X, Zhang Q, Zhang L, Wei W, Liu L, Li B, Zhang L, Zhang Y, Hui Y and Lei Y. Circulating chemerin levels in women with polycystic ovary syndrome: a meta-analysis. Gynecol Endocrinol 2022; 38: 22-27.
[9] Mansoori A, Amoochi-Foroushani G, Zilaee M, Hosseini SA and Azhdari M. Serum and follicular fluid chemerin and chemerin mRNA expression in women with polycystic ovary syndrome: systematic review and meta-analysis. Endocrinol Diabetes Metab 2022; 5: e00307.

[10] Zhang W, Wu Y, Yuan Y, Wang L, Yu B, Li X, Yao Z and Liang B. Identification of key biomarkers for predicting atherosclerosis progression in polycystic ovary syndrome via bioinformatics analysis and machine learning. Comput Biol Med 2024; 183: 109239.

[11] Pratama G, Wiweko B, Asmarinah, Widyahening IS, Andraini T, Bayuaji H and Hestiantoro A. Mechanism of elevated LH/FSH ratio in lean PCOS revisited: a path analysis. Sci Rep 2024; 14: 8229.

[12] Scragg J, Hobson A, Willis L, Taylor KS, Dixon S and Jebb SA. Effect of weight loss interventions on the symptomatic burden and biomarkers of polycystic ovary syndrome: a systematic review of randomized controlled trials. Ann Intern Med 2024; 177: 1664-1674.

[13] Melin JM, Forslund M, Alesi SJ, Piltonen T, Romualdi D, Spritzer PM, Tay CT, Pena AS, Witchel SF, Mousa A and Teede HJ. Effects of different insulin sensitisers in the management of polycystic ovary syndrome: a systematic review and meta-analysis. Clin Endocrinol (Oxf) 2024; 100: 149-163.

[14] Elkind-Hirsch KE, Chappell N, Shaler D, Storment J and Bellanger D. Liraglutide 3 mg on weight, body composition, and hormonal and metabolic parameters in women with obesity and polycystic ovary syndrome: a randomized placebo-controlled-phase 3 study. Fertil Steril 2022; 118: 371-381.

[15] Teede HJ, Tay CT, Laven JJE, Dokras A, Moran LJ, Piltonen TT, Costello MF, Boivin J, Redman LM, Boyle JA, Norman RJ, Mousa A and Joham AE. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Eur J Endocrinol 2023; 189: G43-G64; International PCOS Network.

[16] Miyazaki Y, Matsuda M and DeFronzo RA. Dose-response effect of pioglitazone on insulin sensitivity and insulin secretion in type 2 diabetes. Diabetes Care 2002; 25: 517-523.

[17] Inzucchi SE, Viscoli CM, Young LH, Furie KL, Gorman M, Lovejoy AM, Dagogo-Jack S, Ismail-Beigi F, Korytkowski MT, Pratley RE, Schwartz GG and Kernan WN; IRIS Trial Investigators. Pioglitazone prevents diabetes in patients with insulin resistance and cerebrovascular disease. Diabetes Care 2016; 39: 1684-1692.

[18] Nylander M, Frøssing S, Clausen HV, Kistorp C, Faber J and Skouby SO. Effects of liraglutide on ovarian dysfunction in polycystic ovary syndrome: a randomized clinical trial. Reprod Biomed Online 2017; 35: 121-127.

[19] Knudsen LB and Lau J. The discovery and development of liraglutide and semaglutide. Front Endocrinol (Lausanne) 2019; 10: 155.

[20] Austregésilo de Athayde De Hollanda Morais B, Martins Prizão V, de Moura de Souza M, Ximenes Mendes B, Rodrigues Defante ML, Cosendey Martins O and Rodrigues AM. The efficacy and safety of GLP-1 agonists in PCOS women living with obesity in promoting weight loss and hormonal regulation: a meta-analysis of randomized controlled trials. J Diabetes Complications 2024; 38: 108834.

[21] Balogh Z, Csehely S, Orosz M, Bhattoa HP, Krasznai ZT, Deli T and Jakab A. Relations of insulin resistance, body weight, vitamin D deficiency, SHBG and androgen levels in PCOS patients. Biomedicines 2025; 13: 1803.

[22] Amiri M, Mahmoudieh L, Sheidaei A, Fallahzadeh A and Ramezani Tehrani F. Insulin resistance and idiopathic hirsutism: a systematic review, meta-analysis, and meta-regression. J Cosmet Dermatol 2022; 21: 5346-5359.

[23] Kounatidis D, Vallianou NG, Rebelos E, Kouveletsou M, Kontrafouri P, Eleftheriadou I, Diakoumopoulou E, Karampela I, Tentolouris N and Dalamaga M. The many facets of PPAR-γ agonism in obesity and associated comorbidities: benefits, risks, challenges, and future directions. Curr Obes Rep 2025; 14: 19.

[24] Palavicini JP, Chavez-Velazquez A, Fourcaudot M, Tripathy D, Pan M, Norton L, DeFronzo RA and Shannon CE. The insulin-sensitizer pioglitazone remodels adipose tissue phospholipids in humans. Front Physiol 2021; 12: 784391.

[25] Zheng Z, Zong Y, Ma Y, Tian Y, Pang Y, Zhang C and Gao J. Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. Signal Transduct Target Ther 2024; 9: 234.

[26] Xu Y and Qiao J. Association of insulin resistance and elevated androgen levels with polycystic ovarian syndrome (PCOS): a review of literature. J Healthc Eng 2022; 2022: 9240569.

[27] Rojas J, Chávez M, Olivar L, Rojas M, Morillo J, Mejías J, Calvo M and Bermúdez V. Polycystic ovary syndrome, insulin resistance, and obesity: navigating the pathophysiologic labyrinth. Int J Reprod Med 2014; 2014: 719050.

[28] Stefanaki K, Karagiannakis DS, Peppa M, Vryonidou A, Kalantaridou S, Goulis DG, Psaltopoulou T and Paschou SA. Food cravings and obesity in women with polycystic ovary syndrome: pathophysiological and therapeutic considerations. Nutrients 2024; 16: 1049.

[29] Witchel SF and Tena-Sempere M. The Kiss1 system and polycystic ovary syndrome: lessons from physiology and putative pathophysiologic implications. Fertil Steril 2013; 100: 12-22.

Table S1. Comparison of anthropometric, metabolic, and hormonal parameters between the control and combination groups before and after treatment

Variable	Time	Control group (n=168)	Combination group (n=170)	Between-group *P* value	Between-group Q value[*]	Within-group *P* value (Control)	Within-group Q value[*] (Control)	Within-group *P* value (Combination)	Within-group Q value[*] (Combination)
BMI (kg/m^2)	Pre-treatment	31.47 ± 2.52	31.44 ± 2.67	0.900	0.900	-	-	-	-
	Post-treatment	29.94 ± 2.75	27.55 ± 2.29	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Waist circumference (cm)	Pre-treatment	99.12 ± 7.64	98.12 ± 7.33	0.220	0.220	-	-	-	-
	Post-treatment	93.78 ± 6.51	87.04 ± 6.24	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
FPG (mmol/L)	Pre-treatment	5.62 ± 0.58	5.59 ± 0.55	0.597	0.716	-	-	-	-
	Post-treatment	5.21 ± 0.46	4.75 ± 0.41	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
FINS (mU/L)	Pre-treatment	16.83 ± 2.94	16.94 ± 2.88	0.745	0.812	-	-	-	-
	Post-treatment	12.65 ± 2.15	9.87 ± 1.96	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
HOMA-IR	Pre-treatment	4.21 ± 0.89	4.19 ± 0.91	0.837	0.837	-	-	-	-
	Post-treatment	2.94 ± 0.67	2.08 ± 0.54	<0.001	<0.001	<0.001[†]	<0.001	<0.001	<0.001
TC (mmol/L)	Pre-treatment	4.86 ± 0.51	4.92 ± 0.53	0.353	0.498	-	-	-	-
	Post-treatment	4.52 ± 0.45	4.08 ± 0.39	<0.001[‡]	<0.001	<0.001	<0.001	<0.001	<0.001
TG (mmol/L)	Pre-treatment	1.92 ± 0.34	1.98 ± 0.36	0.142	0.213	-	-	-	-
	Post-treatment	1.68 ± 0.29	1.41 ± 0.22	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
LH (IU/L)	Pre-treatment	12.48 ± 3.02	12.51 ± 3.11	0.941	0.982	-	-	-	-
	Post-treatment	9.23 ± 2.11	7.15 ± 1.86	<0.001	<0.001	<0.001	<0.001	<0.001[††]	<0.001
FSH (IU/L)	Pre-treatment	5.64 ± 0.82	5.58 ± 0.79	0.388	0.518	-	-	-	-
	Post-treatment	5.59 ± 0.78	5.52 ± 0.75	0.418	0.527	0.533	0.586	0.537	0.586
T (nmol/L)	Pre-treatment	2.21 ± 0.45	2.20 ± 0.44	0.989	0.989	-	-	-	-
	Post-treatment	1.73 ± 0.38	1.21 ± 0.29	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
LH/FSH ratio	Pre-treatment	2.23 ± 0.65	2.25 ± 0.67	0.530[‡]	0.586	-	-	-	-
	Post-treatment	1.66 ± 0.48	1.30 ± 0.35	<0.001[‡]	<0.001	<0.001	<0.001	<0.001[††]	<0.001
Chemerin (ng/mL)	Pre-treatment	176.23 ± 42.15	174.75 ± 43.82	0.586[‡]	0.639	-	-	-	-
	Post-treatment	132.56 ± 34.27	117.63 ± 31.45	<0.001[‡]	<0.001	<0.001	<0.001	<0.001	<0.001
Visfatin (ng/mL)	Pre-treatment	9.52 ± 1.48	9.42 ± 1.51	0.461	0.553	-	-	-	-
	Post-treatment	8.01 ± 1.32	7.23 ± 1.18	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Chemerin/Visfatin ratio	Pre-treatment	18.62 ± 3.84	18.58 ± 3.91	0.926	0.926	-	-	-	-
	Post-treatment	16.55 ± 3.21	16.27 ± 3.08	<0.001	<0.001	0.005	0.007	<0.001	<0.001

Note: [*]Q values are Benjamini-Hochberg false discovery rate-adjusted *p*-values for multiple comparisons within each section (anthropometric, glucose metabolism, lipid metabolism, reproductive hormones, and adipokines). [†]Wilcoxon signed-rank test (non-parametric) was used because the difference was not normally distributed. [‡]Mann-Whitney U test was used for between-group comparison (non-parametric). [††]Wilcoxon signed-rank test was used for within-group comparison. Abbreviations: BMI, Body Mass Index; FPG, Fasting Plasma Glucose; FINS, Fasting Insulin; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; TC, Total Cholesterol; TG, Triglycerides; LH, Luteinizing Hormone; FSH, Follicle-Stimulating Hormone; T, Testosterone; PCOS, Polycystic ovary Syndrome.

Table S2. Multivariate logistic regression analysis including interaction between treatment groups and baseline chemerin/visfatin ratio for improvement in insulin resistance

Variable	β	SE	OR (95% CI)	*P* value
Treatment	2.941	1.901	18.939 (0.478-854.660)	0.122
Baseline chemerin/visfatin ratio	0.285	0.073	1.330 (1.160-1.546)	<0.001
Baseline BMI	0.161	0.054	1.175 (1.059-1.308)	0.003
Baseline TG	0.617	0.27	1.854 (1.097-3.172)	0.022
Baseline T	1.107	0.283	3.026 (1.759-5.347)	<0.001
Treatment × baseline chemerin/visfatin ratio	-0.073	0.101	0.930 (0.761-1.131)	0.468

Note: HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, BMI: Body Mass Index, TG: Triglycerides, T: Testosterone, SE: Standard Error, OR: Odds Ratio, CI: Confidence Interval.

Table S3. Multivariate logistic regression analysis including interaction between treatment groups and baseline BMI for improvement in insulin resistance

Variable	β	SE	OR (95% CI)	*P* value
Treatment	-0.631	3.383	0.532 (0.001-401.343)	0.852
Baseline chemerin/visfatin ratio	0.244	0.05	1.277 (1.161-1.412)	<0.001
Baseline BMI	0.124	0.072	1.132 (0.985-1.308)	0.084
Baseline TG	0.625	0.269	1.868 (1.109-3.189)	0.02
Baseline T	1.11	0.284	3.034 (1.761-5.373)	<0.001
Treatment × baseline BMI	0.07	0.107	1.073 (0.870-1.328)	0.512

Note: HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, BMI: Body Mass Index, TG: Triglycerides, T: Testosterone, SE: Standard Error, OR: Odds Ratio, CI: Confidence Interval.