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Original Article

Efficacy and safety of semaglutide combined with metformin in treating T2DM with overweight or obesity: a systematic review and meta-analysis

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Abstract: Objective: To evaluate the efficacy and safety of semaglutide combined with metformin in treating type 2 diabetes mellitus (T2DM) patients who are overweight or obese. Methods: We conducted a comprehensive search across multiple databases including Wanfang, CNKI, Chinese Biomedical Literature, VIP, Embase, PubMed, Cochrane Library, and Web of Science. Studies were screened to include randomized controlled trials (RCTs) comparing semaglutide combined with metformin versus metformin alone in T2DM patients with obesity or who are overweight. Primary outcomes included glycemic efficacy and body mass index (BMI). Secondary endpoints included pancreatic function, blood lipids, and incidence of adverse effects. Pooled and sensitivity analyses were performed, and risk of bias was assessed. Results: Ten studies met the inclusion criteria, all involving oral semaglutide. Compared with placebo, semaglutide with metformin significantly reduced fasting blood glucose (SMD: -0.94; 95% CI: -1.53 to -0.35) and 2-hour postprandial glucose (SMD: -0.97; 95% CI: -1.44 to -1.50; P<0.0001). It also lowered HbA1c levels (SMD: -1.13; 95% CI: -1.85 to -0.42; P<0.001) and BMI (SMD: -1.08; 95% CI: -1.47 to -0.69). Improvements were also noted in HOMA-IR and blood lipid levels. However, there were no significant differences in the incidence of adverse reactions, such as hypoglycemia, gastrointestinal reactions, and dizziness and headache between the two groups (all P>0.05). Conclusion: Treatment with semaglutide combined with metformin significantly improved glycemic control, insulin resistance, weight, BMI, and lipid profiles in patients with T2DM who are overweight or obese.

Keywords: Semaglutide, type 2 diabetes mellitus, obesity, systematic review, meta-analysis

Introduction

Type 2 diabetes mellitus (T2DM) is a common systemic metabolic disease seen in clinical practice, characterized by chronic hyperglycemia. Common clinical manifestations include increased thirst, hunger, urination, and weight loss. T2DM has many complications, affecting various organs, and is associated with high incidence, high mortality, and high disability rates [1, 2]. According to statistics [3], China has the highest number of diabetes cases globally, approximately 114 million. The incidence of T2DM is increasing annually, necessitating prompt and effective treatment.

Being overweight or obese, as a chronic metabolic disease, is a major contributor to the occurrence and development of T2DM. Overweight/obesity not only affects the glucose and lipid metabolism of patients but also exacerbates insulin resistance [4-6]. Clinical evidence suggests that weight management has a significant improvement on blood glucose control, insulin resistance, and beta-cell function in patients with T2DM [7, 8]. According to survey results from 2010, 2013, and 2015-2017 [9], the prevalence of diabetes varies among different body mass index (BMI) groups. The prevalence of diabetes in patients with a BMI<25 kg/m^2 was 6.9%, 7.4%, and 8.8%, while it was 14.3%, 14.7%, and 13.8% in patients with a BMI between 25 kg/m^2 and 30 kg/m^2, and as high as 19.6%, 19.6%, and 20.1% in patients with a BMI≥30 kg/m^2. This trend underscores the link between higher BMI and increased diabetes prevalence. Therefore, for patients being overweight/obese with diabetes, both domestic

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and international guidelines and expert consensus recommend prioritizing weight-neutral or weight-reducing medications when selecting glucose-lowering treatment plans.

Currently, weight loss or weight-neutral antidiabetic drugs mainly include metformin, alpha-glucosidase inhibitors, GLP-1 receptor agonists (GLP-1RA), DPP-4 inhibitors, SGLT-2 inhibitors (SGLT-2i), and insulin analogs. Metformin has the benefits of weight neutrality, improved lipid profile, and reduced platelet aggregation, which can improve vascular complications of diabetes. Its safety has been well-established through 60 years of clinical experience and trial data [10]. Given the safety, efficacy, and cost advantage compared to newer drugs, guidelines support metformin as a first-line treatment for most diabetes patients. SGLT-2 inhibitors are highly valued in glycemic management due to their weight loss effects and cardiovascular and renal protection. A study comparing relevant indicators before and after SGLT-2 inhibitor treatment in pre-obese T2DM patients found significant reductions in weight, BMI, fasting blood glucose (FBG), and glycated hemoglobin after 24 weeks of treatment. GLP-1 receptor agonists are also noteworthy for their efficacy in glycemic control and weight loss, alongside providing cardiovascular benefits. The 2019 European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD) guidelines [11] recommend GLP-1 receptor agonists as one of the preferred monotherapy options for T2DM patients with atherosclerotic cardiovascular disease (ASCVD) or high/very high cardiovascular risk factors. Obesity is closely related to insulin resistance, and it appears that the conventional approach of combining oral antidiabetic drugs with intensified insulin therapy may not be optimal for overweight/obese T2DM patients.

Sernaglutide, a glucagon-like peptide-1 (GLP-1) analogue, is approved (at doses up to 1 mg, subcutaneous administration, once weekly) for the treatment of T2DM, and is recommended as a second-line therapy after metformin [12]. Furthermore, meta-analyses of randomized controlled trials (RCTs) of semaglutide in patients with T2DM have shown benefits on glycemic control and weight loss [13]. Recently, the US Food and Drug Administration (FDA) approved semaglutide for patients with obesity or those who are overweight [14]. Nevertheless, there is still a lack of comprehensive evaluation of the available evidence to support the effect and safety of semaglutide combined with metformin for patients with T2DM who are overweight or obese in clinical practice.

Therefore, this study comprehensively assessed the effect and safety of semaglutide combined with metformin for overweight or obese patients with T2DM, aiming to provide evidence-based guidance for clinical practice.

Methods

Data sources

Eligible publications were identified through electronic searches across several databases, including Wanfang, CNKI, Chinese Biomedical Literature, VIP, Embase, PubMed, Cochrane Library, Web of Science from their inception to December 2023. The search strategy incorporated a combination of MeSH terms and keywords: (((“Obesity”[Mesh]) OR ((((((obese[Title/Abstract]) OR (fat[Title/Abstract])) OR (obe*[Title/Abstract])) OR (adiposity[Title/Abstract])) OR (overweight[Title/Abstract])) OR (over weight[Title/Abstract])))) AND ((“semaglutide”[Supplementary Concept]) OR ((metformin[Title/Abstract]) AND ((“type 2 diabetes mellitus”[Supplementary Concept]) OR ((“type 2 diabetes”[Supplementary Concept]) AND ((randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract])).

Inclusion and exclusion criteria of literature

Inclusion criteria: 1) Study type: randomized controlled trial (RCTs) or quasi-randomized controlled trial; 2) Study population: patients with T2DM and being overweight/obese; 3) Treatment plan: comparisons involving semaglutide with or without metformin; 4) Outcome measure: changes in blood glucose levels, pancreatic function, and body weight; 5) Publication type: peer-reviewed journal article in English language. Exclusion criteria: 1) Non-randomized controlled trial, such as a single-arm study; 2) Studies on patients aged 3-18 years, animal studies, case reports, or non-primary literature; 3) Studies with incomplete data, duplicate publications, review articles, gray literature where the original article could not be retrieved, or lit-

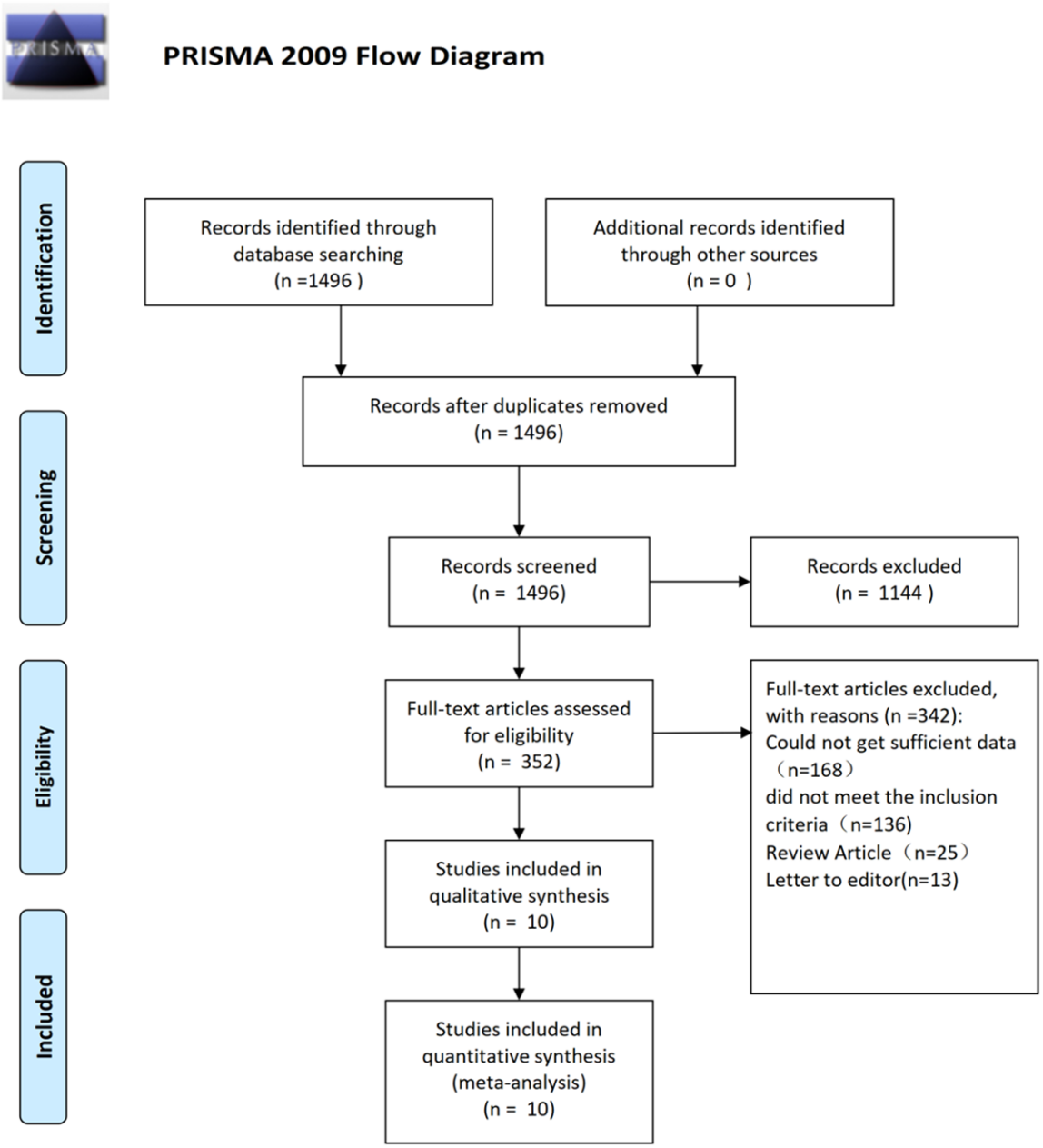

Figure 1. Flow diagram of literature search process.

erature where the outcome indicator was not related to the specified conditions.

Literature screening and data extraction

Two researchers (Juan Li and Kui Li) independently assessed the eligibility of studies based on the inclusion and exclusion criteria outlined above. Both researchers started by examining the titles and abstracts. If a definitive conclusion about a study's eligibility could not be drawn from the title and abstract alone, they proceeded to a full-text review. For studies that met the inclusion criteria, the researchers conducted data selection and assessed the quality of the literature. Discrepancies in the inclusion or exclusion decisions were resolved through discussion or, if necessary, by involving a third-party arbitrator, Jie Zhang.

Evaluation of literature quality

Two researchers (Juan Li and Kui Li) evaluated the quality of the literature according to the

Table 1. Basic characteristics of the included literature

First author/year	Country	Subjects (EG/CG)	Interventions (EG/CG)	NOS score	Outcome indicators	Follow up (Months)
Chen 2023 [16]	China	20/20	EG: semaglutide combined with metformin CG: metformin	7	Fasting Blood Glucose (FBG), Postprandial 2-hour Blood Glucose (2h PG), Glycated Hemoglobin (HbA1c), Body Mass Index (BMI) levels, and gastrointestinal adverse reactions	3
Fang 2023 [17]	China	50/50	EG: semaglutide combined with metformin CG: metformin	7	Fasting Blood Glucose (FBG), Postprandial 2-hour Blood Glucose (2h PG), HOMA-IR, Body Mass Index (BMI) levels, and gastrointestinal adverse reactions	3
Li 2023 [18]	China	40/40	EG: semaglutide combined with metformin CG: metformin	8	Fasting Blood Glucose (FBG), Postprandial 2-hour Blood Glucose (2h PG), HOMA-IR, Body Mass Index (BMI) levels, and gastrointestinal adverse reactions	3
Liu 2023 [19]	China	42/42	EG: semaglutide combined with metformin CG: metformin	6	Fasting Blood Glucose (FBG), Postprandial 2-hour Blood Glucose (2h PG), HOMA-IR	3
Shi 2024 [20]	China	66/66	EG: semaglutide combined with metformin CG: metformin	7	Fasting Blood Glucose (FBG), Postprandial 2-hour Blood Glucose (2h PG), HOMA-IR	2
Wu 2023 [21]	China	40/40	EG: semaglutide combined with metformin CG: metformin	8	Fasting Blood Glucose (FBG), Postprandial 2-hour Blood Glucose (2h PG), Glycated Hemoglobin (HbA1c), Body Mass Index (BMI) levels, and gastrointestinal adverse reactions	3
Xia 2023 [22]	China	30/30	EG: semaglutide combined with metformin CG: metformin	6	Fasting Blood Glucose (FBG), Postprandial 2-hour Blood Glucose (2h PG), Glycated Hemoglobin (HbA1c), Body Mass Index (BMI) levels, and gastrointestinal adverse reactions	5
Zhang 2023 [23]	China	88/86	EG: semaglutide combined with metformin CG: metformin	8	Fasting Blood Glucose (FBG), Postprandial 2-hour Blood Glucose (2h PG), Glycated Hemoglobin (HbA1c), Body Mass Index (BMI) levels	3
Zhang 2024 [24]	China	80/80	EG: semaglutide combined with metformin CG: metformin	7	Fasting Blood Glucose (FBG), Postprandial 2-hour Blood Glucose (2h PG), Glycated Hemoglobin (HbA1c), Body Mass Index (BMI) levels, and gastrointestinal adverse reactions	3
Zhao 2023 [25]	China	26/26	EG: semaglutide combined with metformin CG: metformin	8	Fasting Blood Glucose (FBG), Postprandial 2-hour Blood Glucose (2h PG), Glycated Hemoglobin (HbA1c), Body Mass Index (BMI) levels, and gastrointestinal adverse reactions	3

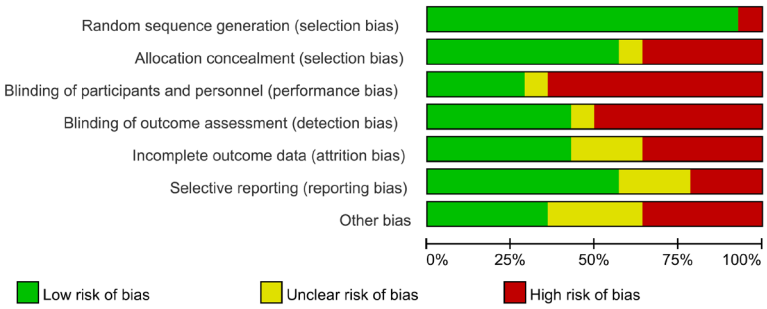

Figure 2. The assessment of risk of bias of included studies.

Jadad scale [15], including the selection of the study population, outcome measures, and comparability between groups. Any disagreements during the evaluation process were resolved through internal group discussions.

Risk of bias assessment

Risk of bias assessment within studies was assessed for the primary outcome by two reviewers independently using the revised Cochrane Collaboration's Risk of Bias Tool (ROB) version 2.0 [15]. Any disagreement was resolved by consensus. Overall risk of bias for each eligible study was considered low if all individual domains were rated as low risk; otherwise, it was considered high risk if any domain was judged to be at high risk of bias. Studies were noted as having 'some concern' in all other situations.

Statistical methods

All analyses were performed using Review Manager (RevMan 5.3, Nordic Cochrane Center, Copenhagen, Denmark) and Stata 13.1 (StataCorp, College Station, Texas). Weighted mean difference (WMD) and 95% confidence intervals (CI) for continuous variables were calculated using the inverse variance method. For some included studies that only provided standard error (SE) data, the standard deviation (SD) was calculated using the equation $SD=SE/\sqrt{N}$ (N represents the sample size). Continuous outcome variables (HbA1c, FPG, and weight changes) were converted to international standard units (% for HbA1c, mmol/L for FPG, and kg for weight) before merging the data. The results of the statistical analysis of clinical outcome variables were presented as forest plot. Each effect size and its corresponding 95% CI were represented by a horizontal line, with the length of the line indicating the range of the CI. The square marker in the middle of the line represented the effect size, and the middle line indicated that the WMD at that point was 0. The diamond symbol represented the results of the meta-analysis. A significance level of 0.05 was used, and when the short line or diamond symbol intersected with the middle line, it indicated that the *P*-value was greater than 0.05 or the 95% CI included 0 (WMD), suggesting that the difference was not statistically significant.

Results

Literature search and study characteristics

Results of the study selection process are depicted in **Figure 1**. A total of 10 studies, involving 962 patients, were included in this meta-analysis [16-25]. The characteristics of studies included are shown in **Table 1**. These studies were conducted in China. Randomization was performed according to a computer-generated random list or by means of a randomly generated number pattern in most of the trials [16-25]. Overall, the quality of these studies was rated as moderate to high (**Figure 2**).

Efficacy of semaglutide combined with metformin on glycemic control

Nine studies [16, 18-25] compared efficacy of semaglutide combined with metformin and metformin alone in glycemic control, and the results demonstrated that semaglutide combined with metformin exhibited a more pronounced reduction in FBG compared with metformin alone (SMD: -0.94; 95% CI=[-1.53, -0.35]; I^2=93.8%; P<0.001) (**Figure 3**). A total of 7 studies [18, 19, 21-25] compared the 2 hour post prandial glucose between two arms and the results indicated that semaglutide combined with metformin resulted in a more significantly reduced 2 hour post prandial glucose level (SMD: -0.97; 95% CI=[-1.44, -1.50]; I^2=88.1%; P<0.0001) (**Figure 4**). Furthermore, 6 studies [18, 21-25] reported the efficacy of semaglutide combined with metformin on

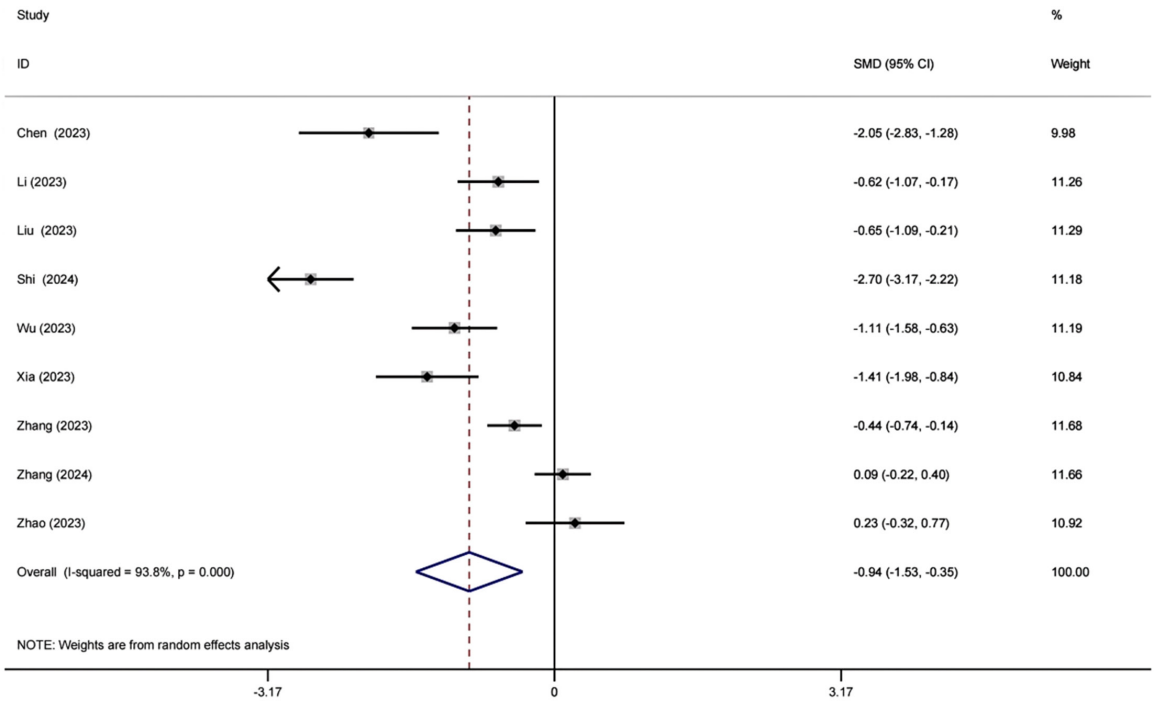

Figure 3. Forest plot on the fasting blood glucose.

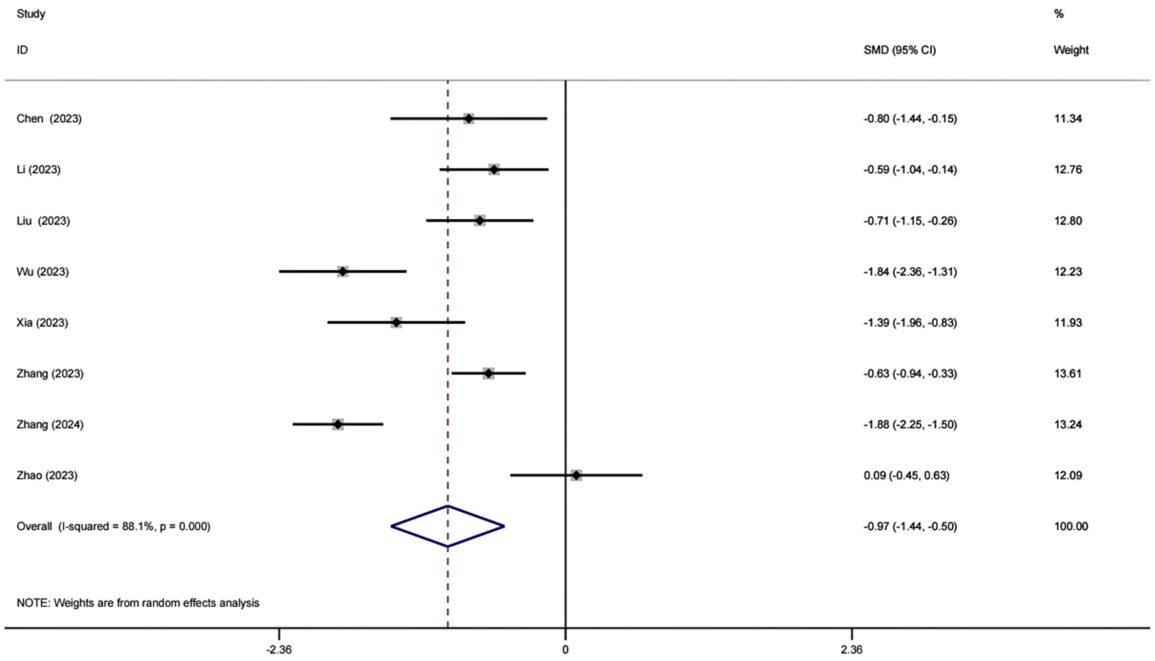

Figure 4. Forest plot on the 2 hour post prandial glucose.

HbA1c, and the results showed that the combined treatment reduced the HbA1c level more obviously than the metformin alone (SMD: -1.13; 95% CI=[-1.85, -0.42]; I^2=93.8%; P<0.001) (**Figure 5**).

Efficacy of semaglutide combined with metformin on BMI reduction

Six studies [17, 18, 21, 22, 24, 25] reported the effect of semaglutide combined with metfor-

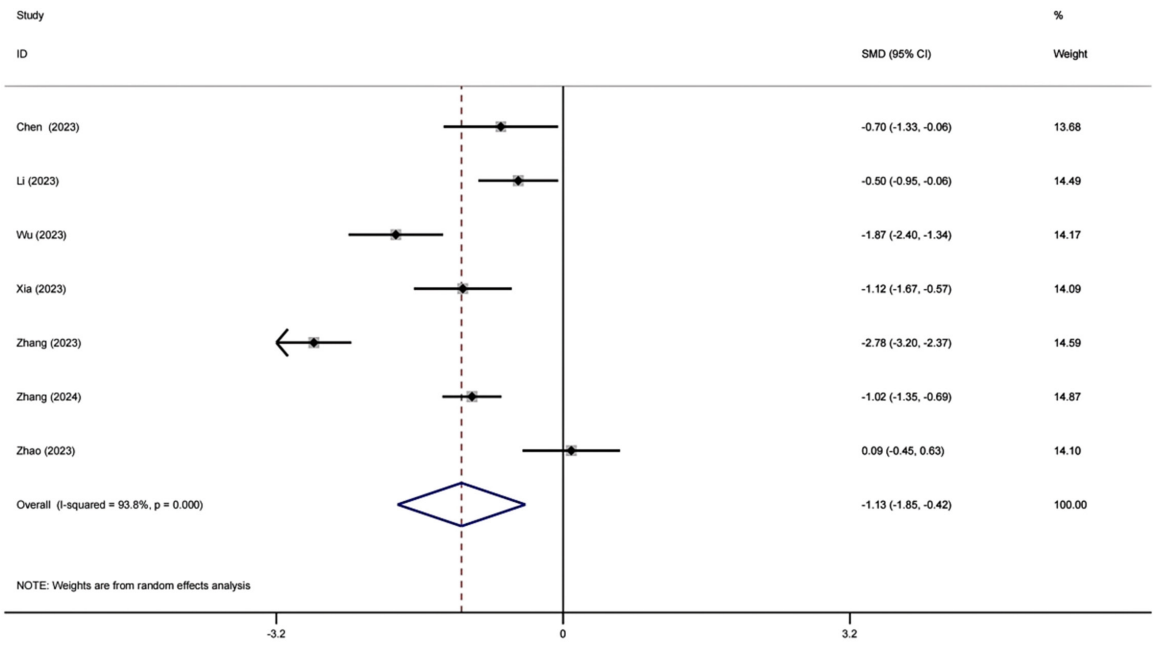

Figure 5. Forest plot on HbA1c.

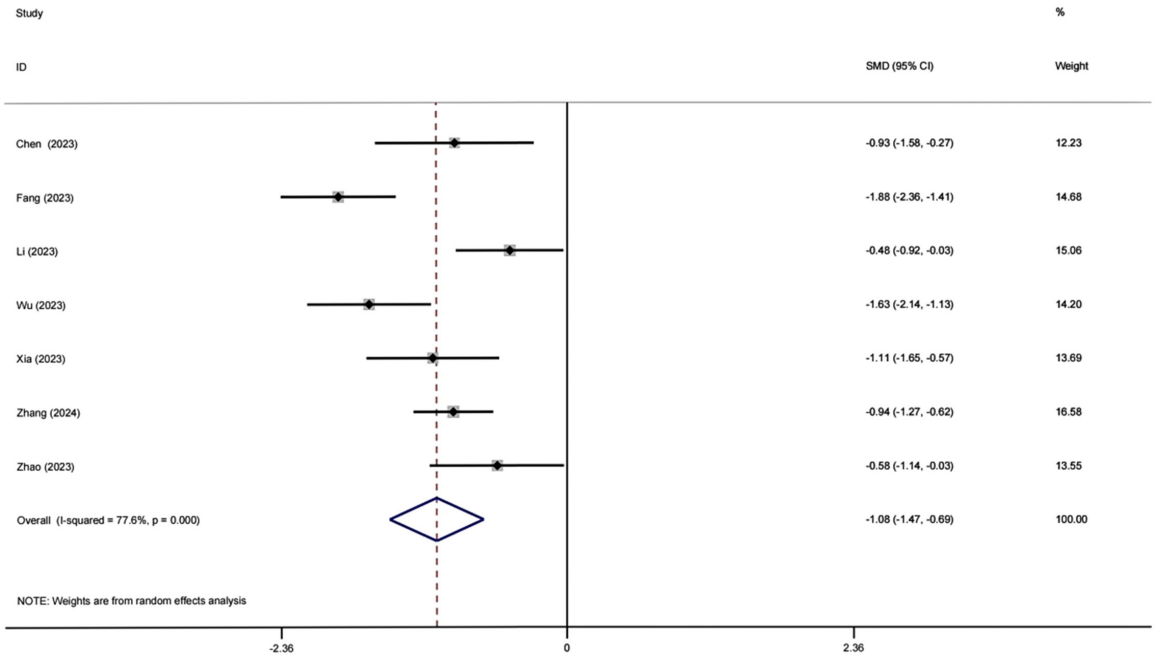

Figure 6. Forest plot on BMI.

min on BMI, and the results showed that the combined treatment resulted in a lower BMI compared to metformin alone (SMD: -1.08; 95% CI=[-1.47, -0.69]; I^2=77.6%; P<0.0001). Notably, the results were consistent across different doses, and heterogeneity did not decrease in a sensitivity analysis that excluded any studies, as depicted in **Figure 6**.

Efficacy of semaglutide combined with metformin on pancreatic function

Meta-analysis of data from the 9 eligible studies [17-25] showed that homeostatic model assessment of insulin resistance (HOMA-IR) were significantly improved in T2DM patients who are overweight or obese (SMD=-0.92; 95%

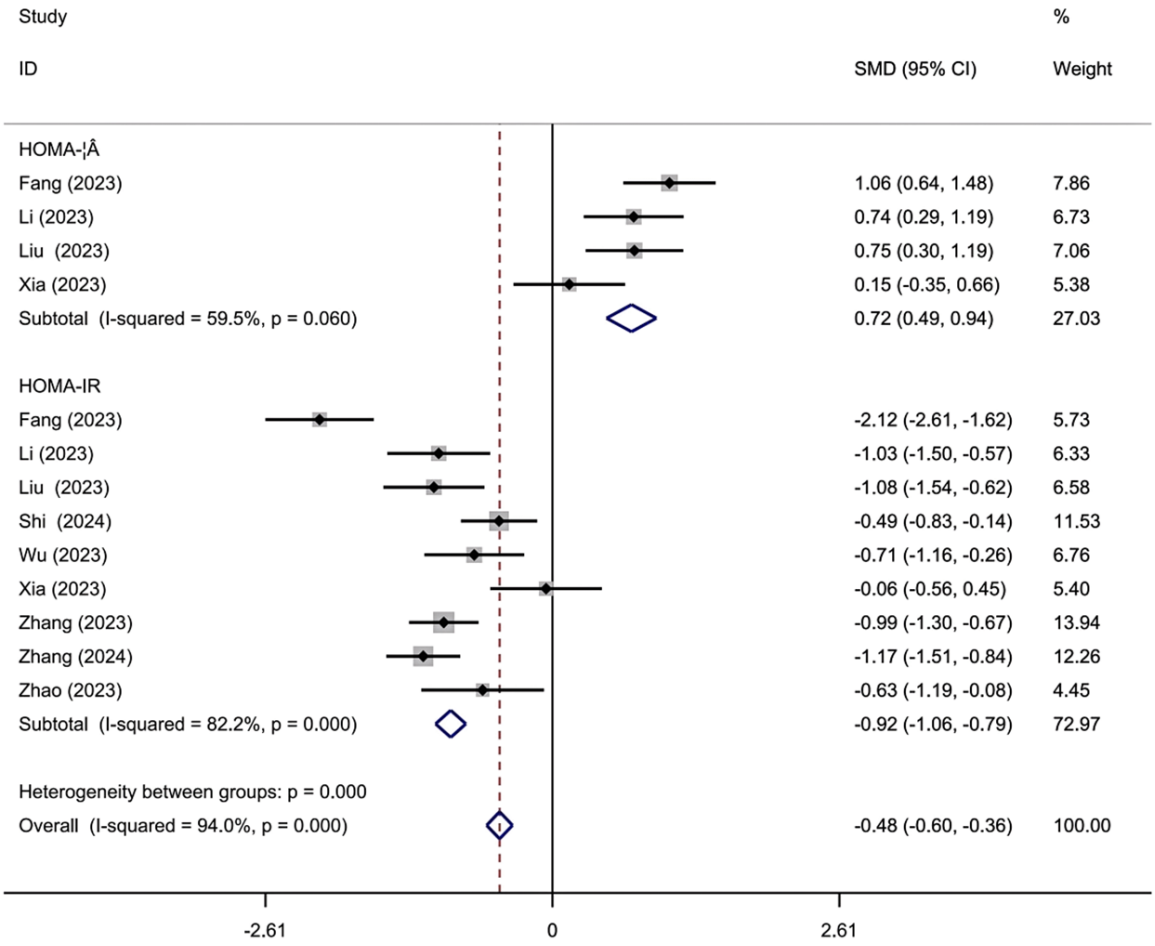

Figure 7. Forest plot on pancreatic function.

CI=[-1.06, -0.79]; P<0.0001, **Figure 7**). Moreover, we also analyzed the effect of semaglutide combined with metformin on HOMA-β. As shown in **Figure 7**, four studies [17-19, 22] reported the results of HOMA-β, demonstrating that HOMA-β of two groups had no significant difference (SMD=-0.72; 95% CI=[0.49, 0.94]; P=0.06).

Efficacy of semaglutide combined with metformin on blood lipids

There were 4 [18, 19, 21, 23] and 5 studies [18-21, 23] reporting on the effects of semaglutide combined with metformin on TC and TG, respectively. Compared to metformin alone group, semaglutide combined with metformin led to more significant reductions in TC (SMD: -1.03; 95% CI=[-1.49, -0.56]; I^2=93.9%; P< 0.001) and TG (SMD: -0.96; 95% CI=[-1.56, -0.36]; I^2=87.6%; P<0.001) (**Figure 8**).

Comparison of adverse reactions between semaglutide combined with metformin and metformin alone cohorts

As shown in **Figure 9**, the results of adverse reactions, such as hypoglycemia, gastrointestinal reactions and dizziness and headache, between the two groups had no significant difference (SMD=1.58, 95% CI=[0.47, 5.25], P=0.736; SMD=2.28, 95% CI=[1.2, 4.35], P=0.993; and SMD=0.74, 95% CI=[0.29, 1.89], P=0.571, respectively).

Publication bias

The funnel plots for each meta-analysis are shown in **Figure 10**. The symmetry observed in these plots, with most studies aligning near the central axis, indicates relatively low levels of publication bias.

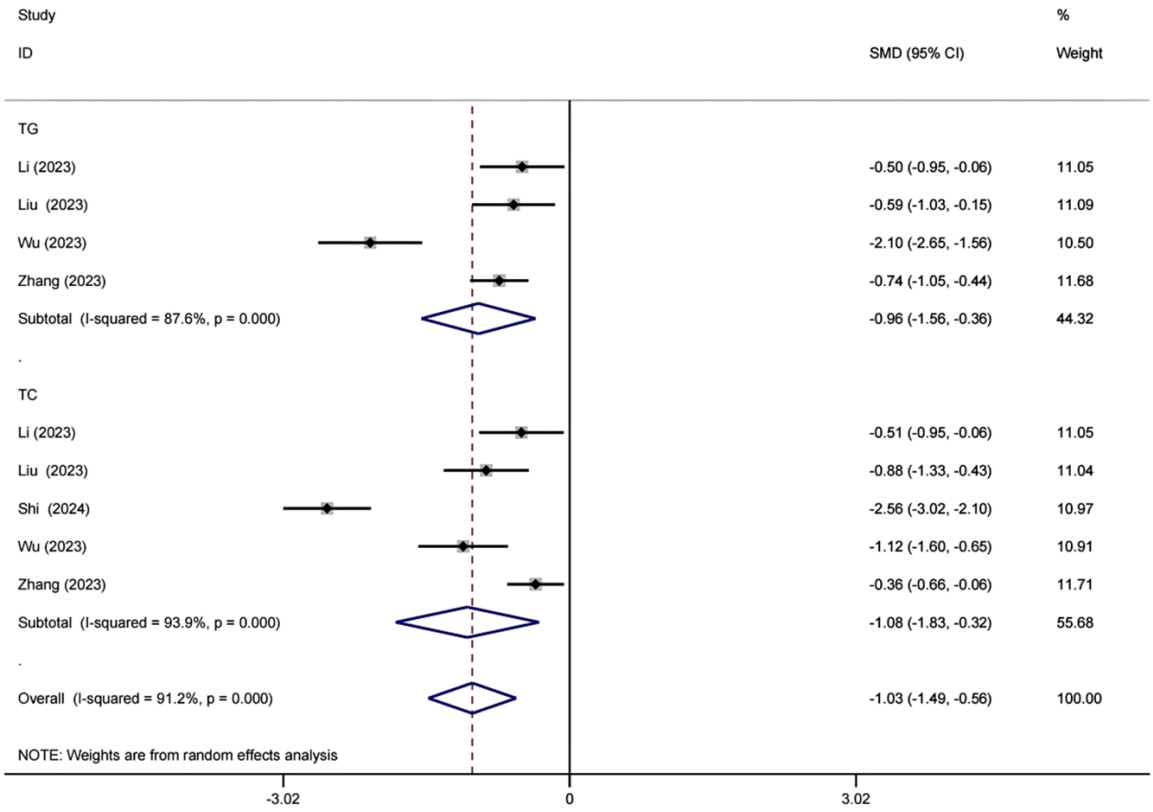

Figure 8. Forest plot on blood lipids.

Discussion

This study conducted a meta-analysis to assess the efficacy of semaglutide combined with metformin in patients with type 2 diabetes mellitus (T2DM) while being overweight or obese. Key indicators such as glycated hemoglobin (HbA1c), fasting blood glucose (FPG), HOMA IR, body mass index (BMI), and lipid levels were evaluated to determine the improvement in insulin resistance syndrome.

In terms of blood glucose control, the meta-analysis study showed that semaglutide combined with metformin demonstrated a better hypoglycemic effect, with significant reductions in FPG and HbA1c. Some studies suggest that high dose semaglutide is associated with a more pronounced decrease in FPG compared to the lower doses [26]. Therefore, it is still unclear whether semaglutide or glargine insulin is more effective in reducing FPG.

In terms of regulating fasting insulin, the meta-analysis shows that semaglutide combined with metformin did not effectively regulate fasting insulin as the control group did. However, it significantly improved the HOMA IR. This may be because insulin resistance is not only related to fasting insulin concentration but also to changes in fasting plasma glucose (FPG) [27]. This study found no significant change in fasting insulin concentration, but FPG decreased significantly, suggesting an increase in insulin sensitivity. This conclusion is consistent with previous research results [28]. However, the number of studies included in this meta-analysis is limited, and further evaluation research is needed by including more high-quality studies in the future.

In terms of BMI, the meta-analysis studies showed that the combination of semaglutide and metformin significantly reduced BMI compared to the control arm. The research results are consistent with the weight-reducing mechanism of semaglutide, as it helps decrease patient weight and lower BMI by affecting appetite and satiety, improving insulin resistance, and effectively regulating blood glucose levels.

The results of this meta-analysis suggest that patients in the semaglutide and metformin group showed a more significant decrease in

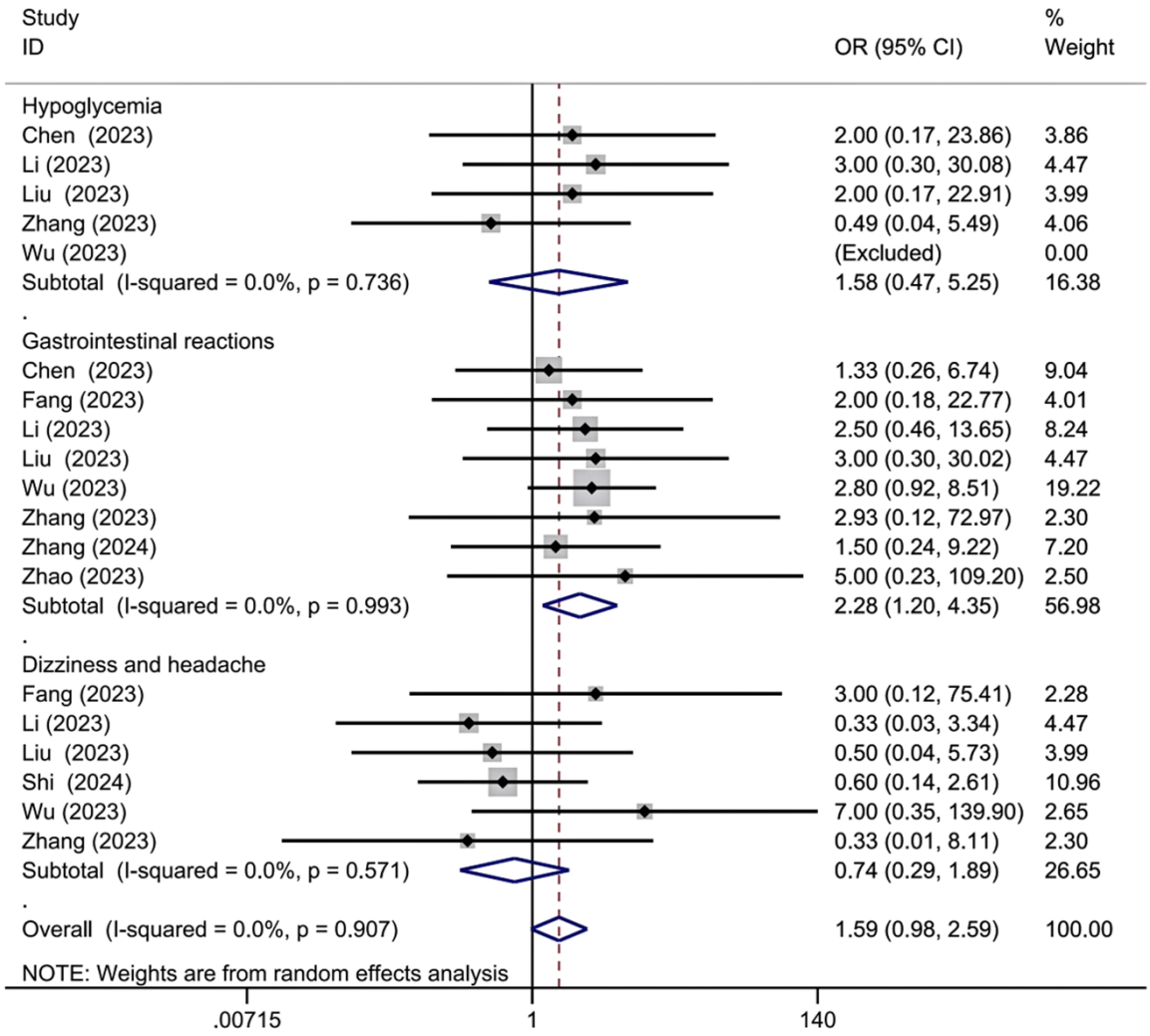

Figure 9. Forest plot on adverse reactions.

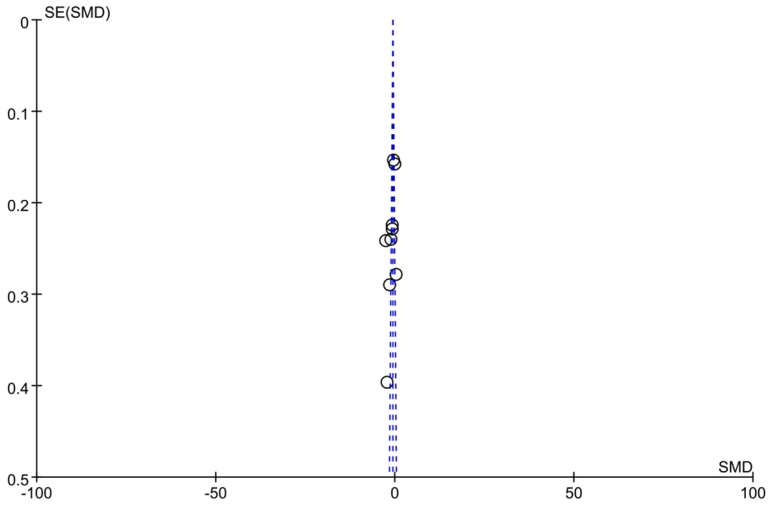

Figure 10. Publication bias.

TC and TG compared to the control arm. This effect may be linked to the higher baseline lipid levels typically seen in overweight or obese patients and the influence of semaglutide and metformin on dietary habits [29]. Studies have shown a significant positive correlation and causal relationship between blood glucose, lipid levels, and blood pressure, all of which are factors affecting insulin resistance [30-33]. Other studies have shown that if blood lipids and blood pressure are well controlled in patients

with T2DM, it not only significantly delays the occurrence of microvascular complications of diabetes, but also significantly reduces the risk of cardiovascular and cerebrovascular accidents related to diabetes [34-36]. Therefore, semaglutide, through its good regulation of lipid levels, increases insulin sensitivity in patients, effectively controls blood glucose, and slows down the progression of acute and chronic complications in patients with T2DM and issues with being overweight/obese. It can be considered as a new medication option for these patients.

However, this study has limitations as we only included studies of Chinese origin. Also, our results are primarily based on indirect comparisons, as most studies compared active drugs against placebo with a lack of head-to-head comparisons. Some trials had a short duration and a small sample size.

This systematic review focused on the efficacy and safety of semaglutide combined with metformin in T2DM patients being overweight or obese in randomized clinical trials. Our findings suggest that semaglutide combined with metformin results in more substantial reductions in glycated hemoglobin, fasting blood glucose, HOMA IR, BMI, and lipid levels compared to metformin alone.

Disclosure of conflict of interest

None.

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