Iran J Public Health, Vol. 54, No.7, Jul 2025, pp.1350-1363

Review Article

The Efficacy and Safety of Hypoglycemic Agents in the Middle-Aged and Elderly Patients with Diabetes Mellitus: A Systematic Review and Meta-Analysis

*Jiayan Huang [1], Huawei Qiu [1], *Kaishun Meng [2]*

1. *Department of Pharmacy, Guangdong Provincial Hospital of Chinese Medicine, Hainan Hospital, Haikou City, Hainan Province, China*
2. *Department of Geriatrics, Sanya People's Hospital, West China (Sanya) Hospital, Sichuan University, Sanya City, Hainan Province, China*

***Corresponding Author:** Email: mengkaishun1336@163.com

(Received 15 Feb 2025; accepted 12 May 2025)

Abstract

Background: We aimed to evaluate the efficacy and safety of combined hypoglycemic agents and insulin therapy in the middle-aged and elderly patients with diabetes through a meta-analysis.

Methods: Literature was searched in PubMed, Cochrane Library, EMbase, Web of Science, WanFang, VIP, and CNKI databases for studies on the combined use of hypoglycemic agents and insulin therapy in the middle-aged and elderly patients with diabetes, with a search time limit up to February 2023.

Results: This article includes 8 RCTs. The risk of bias assessment shows that one article had a low risk of bias, one article have an unclear risk of bias, and 6 articles have a high risk of bias. The meta-analysis results show that the combination of hypoglycemic agents and insulin has better blood glucose control (P=0.0001); fasting blood glucose reduction is more significant (P<0.00001); the 2-hour postprandial blood glucose reduction is more noticeable (P=0.002); HbA1c reduction is more pronounced (P=0.005); however, there is no difference in the incidence of adverse reactions between the two groups (P=0.09).

Conclusion: The combination of hypoglycemic agents and insulin in the treatment of middle-aged and elderly diabetic patients can reduce the fasting blood glucose, the 2-hour postprandial blood glucose, and HbA1c, and reduce adverse reactions. However, due to the limitations in the number and quality of the included studies, the conclusion still requires further verification from more high-quality RCTs.

Keywords: Hypoglycemic agents; Insulin; Middle-aged and elderly; Diabetes mellitus

Introduction

Diabetes, as a chronic endocrine disease, has a higher prevalence in middle-aged and elderly populations, severely affecting their physical health and quality of life. In recent years, with the improvement of living standards and medical conditions, the aging population has increased, and the incidence of diabetes has also risen (1,2). Diabetes is a widespread metabolic disorder caused by various factors, including insulin secretion defects, insulin resistance in insulin-sensitive

tissues, aging, and environmental factors such as stress and obesity (3-4). This disease can lead to various complications, including cardiovascular diseases, dyslipidemia, and renal failure (5). The goal of diabetes treatment is to safely achieve and maintain blood glucose control to reduce the risk of microvascular and macrovascular complications and, in the long run, lower diabetes-related mortality. However, as the disease progresses, achieving near-normal blood glucose control becomes increasingly difficult, and most patients eventually require insulin treatment (6). Insulin, either alone or in combination with oral hypoglycemic agents, can improve glucose metabolism in the body. However, when using relatively large doses of insulin, there is a risk of increased hypoglycemia (7).

The clear treatment goals for middle-aged and elderly diabetic patients are controlling blood glucose and reducing glycosylated hemoglobin levels (8-10). In fact, due to the coexistence of high blood glucose and macrovascular complications in the aged population, patients have a greater risk of hypoglycemia when intensifying blood glucose control (11). Moreover, due to polypharmacy, drug-drug and drug-disease interactions are more likely to occur. Thus, choosing hypoglycemic agents for middle-aged and elderly patients remain a controversial issue. Although some studies show that combining hypoglycemic agents with insulin can significantly improve blood glucose control in aged diabetic patients (12-13), this conclusion does not seem to have universal support (10-14). On the other hand, combined use may increase the susceptibility of middle-aged and elderly diabetic patients and lead to some adverse reactions (9, 15-18).

Therefore, we systematically evaluated the effectiveness and safety of combining hypoglycemic agents with insulin on the treatment of the middle-aged and elderly diabetic patients, aiming to provide a basis for rational clinical medication use.

Materials and Methods

Inclusion and exclusion criteria

Experimental group patients received insulin combined with hypoglycemic agent (metformin, glyburide, nateglinide, and acarbose); control group patients received insulin combined with placebo treatment.

1) Blood glucose control rate (Blood glucose control rate = Number of people under blood glucose control/total number of patients, The target for blood glucose control is a fasting blood glucose level of less than 7.0 mmol/L (126 mg/dL) and a blood glucose level of less than 10.0 mmol/L (180 mg/dL) 2 hours after meals and a hemoglobin a1c (HbA1c) level of less than 7%); 2) Fasting blood glucose (mmol/L); 3) 2-hour postprandial blood glucose (mmol/L); 4) Glycated hemoglobin (HbA1c, %); 5) Incidence of adverse reactions.

The inclusion criteria were as follows: 1) Studies that investigated the association between the efficacy and safety of combined hypoglycemic agents and insulin therapy in middle-aged and elderly patients with type 2 diabetes through a meta-analysis. 2) Randomized controlled trials (RCTs), and the patients diagnosed with diabetes, aged ≥50 years. 3) Diagnostic criteria for diabetes were specified while meeting the conditions for the combination of effect values in the meta-analysis, thereby providing the corresponding effect values and 95% confidence intervals (CIs).

The exclusion criteria were as follows: 1) Unpublished literature, dissertations, conference abstracts, reviews, literature reviews, treatises, and case reports. 2) Studies without the specific information of the research design. 3) Studies with research topic irrelevant to the efficacy and safety of combined hypoglycemic agents and insulin therapy in middle-aged and elderly patients with diabetes. 4) Articles with only hypoglycemic agent combined with insulin group, without control group. 5) Articles with missing data or data that cannot be extracted. 6) Duplicate publications.

Literature search strategy

Computer searches of PubMed, Cochrane Library, EMbase, Web of Science, WanFang, VIP, and CNKI databases were conducted to collect published RCTs on combination therapy with hypoglycemic agents and insulin for diabetes in middle-aged and elderly patients. The search languages were limited to English and Chinese, and the search period was from the database inception to February 2023. The database search was carried out using a combination of subject terms and free words. Chinese and English search terms were both included hypoglycemic agents, metformin, glyburide, nateglinide, acarbose, insulin, diabetes, middle-aged, elderly, effects, adverse reactions.

Literature screening and data extraction

Two researchers independently screened and extracted data according to the following measures: First, carefully reviewing titles and excluding literature unrelated to the research topic. Second, thoroughly reading the abstracts and full texts of the remaining literature to determine whether to include them in the study. Finally, if necessary, contacting the original researchers to obtain uncertain information. In addition, the extracted data included the basic information of the study (such as author, and year of publication), baseline characteristics of the study subjects and intervention measures, bias risk assessment points of concern, and the original data of the outcome indicators of interest.

Bias risk assessment of included studies

We used a randomized controlled trial (RCT) risk assessment tool recommended by the Cochrane Collaboration in included studies. The evaluation tool covers seven key areas: random sequence generation, assignment concealment, implementation of double-blind methods (including participant and researcher blinding), blinding of results evaluation, processing of incomplete results data, selective results reporting, and other potential sources of bias, thus providing a comprehensive reflection of the quality of trial design, implementation, and reporting. The evaluation was performed independently by two researchers, and the results were then crosschecked to ensure the objectivity and accuracy of the evaluation.

Statistical methods

Continuous data were analyzed using the standard mean difference (SMD) and 95% CI, while binary variables were analyzed using the risk ratio (RR) and 95% CI. Heterogeneity among the included studies was assessed using the Chi^2 test and I^2 test. Considering that the literature comes from different countries and regions, we adopted random effects model regardless of heterogeneity. The regression coefficient is treated as a random variable. A funnel plot was used to assess publication bias among the included studies. A two-sided $P < 0.05$ was considered statistically significant. Statistical analysis was performed using RevMan 5.3 software.

Results

Literature screening process

Through the initial search, 2321 eligible articles were obtained. Finally, 8 eligible RCTs were included (Fig. 1).

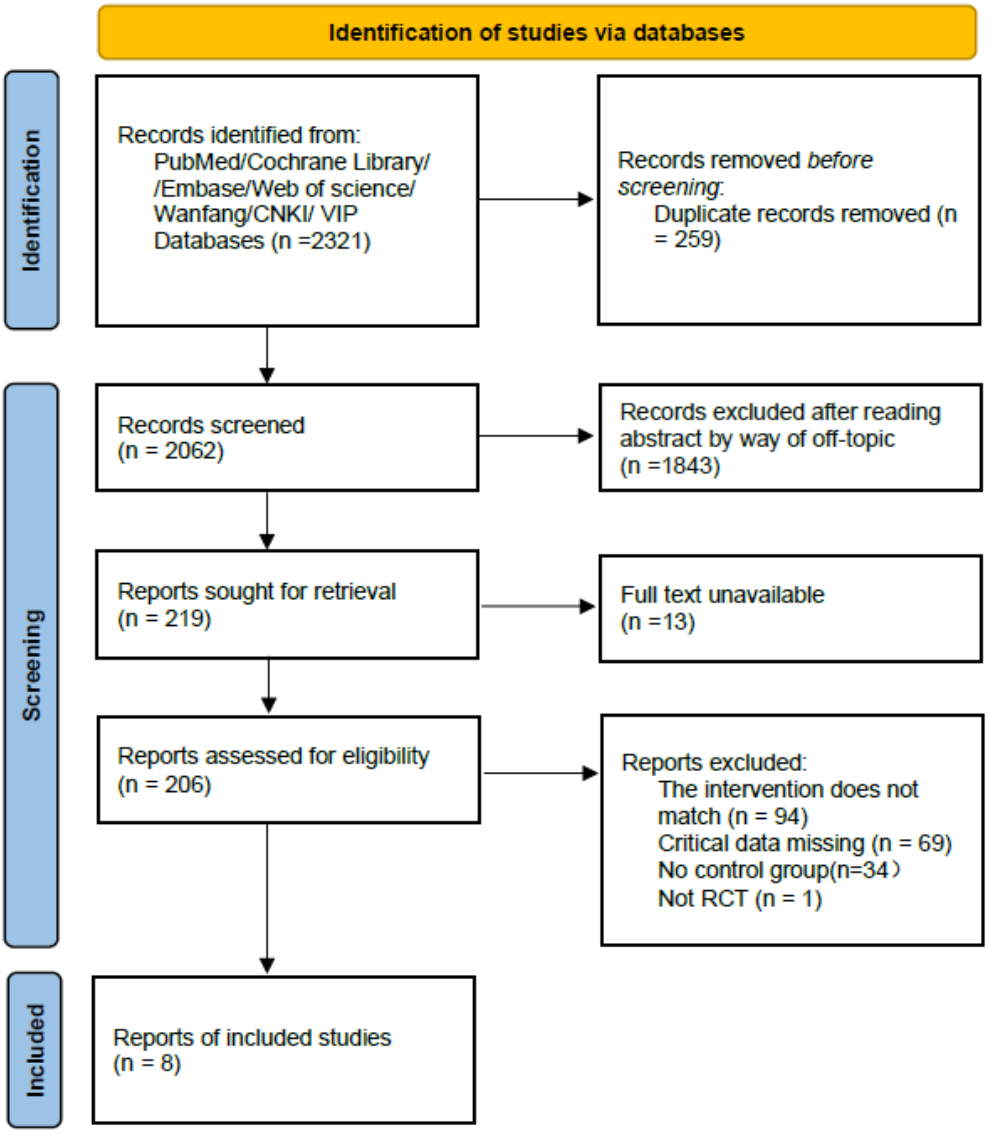

Fig. 1: Literature screening process and results

Basic characteristics of included literature

The basic characteristics of the included literature are shown in Table 1. The publication years of the included studies were from 2007 to 2021, and five of the studies were conducted in China.

Table 1: Basic characteristics of the included literature

Author	Year of publication	Country	Sample size		Age (years)		BMI (kg/m²)		Follow-up time	Ending indicators
			Experimental group	Control group	Experimental group	Control group	Experimental group	Control group		
Chen (17)	2021	China	44	44	50.57±5.34	50.63±5.35	/	/	3 months	① ②③④⑤
Cui (12)	2015	China	55	55	58±9	61±9	24±6	25±2	1year	① ②③④⑤
Dashora (8)	2007	UK	26	29	65.8±9.2	65.5±8.9	31.0 ± 4.0	30.9 ± 5.5	/	① ④⑤
Janka (9)	2007	Germany	67	63	69.3±2.8	69.6±4.1	28.9±3.4	28.9±3.3	/	② ④⑤
Li (15)	2019	China	72	72	68.41±4.46	68.92±4.75	/	/	/	③ ③④⑤
Liu (13)	2016	China	50	50	57.1 ± 6.4	57.4 ±6.2	/	/	3 months	② ③④⑤
Mu (10)	2012	China	58	67	62.6±4.7	62.3±4.6	25.0±2.6	25.3±2.5	1year	① ②③④⑤
Yilmaz (14)	2007	Turkey	15	19	62.6±6.6	61.5±12.0	31.3±3.7	28.2±5.9	0.5 years	②③④

Note: 1, BMI: Body Mass Index (BMI); 2, "/" indicates missing data.
3, Outcome indicators: (1) Blood glucose control rate; (2) Fasting blood glucose; (3) 2-hour postprandial blood glucose; (4) Glycated hemoglobin (HbA1c); (5) Adverse reaction incidence rate. Measurement data are expressed in the form of mean and standard deviation

Risk of bias assessment of included literature

The risk of bias assessment shows that one article had a low risk of bias, one article had an unclear risk of bias, and 6 articles had a high risk of bias, as shown in supplementary Fig. S1 and S2.

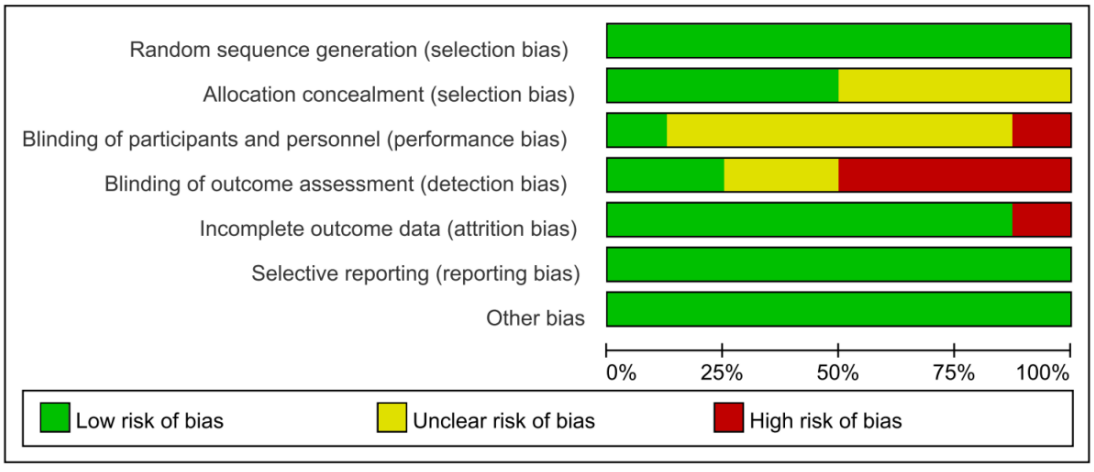

Fig. S1: Risk of bias graph

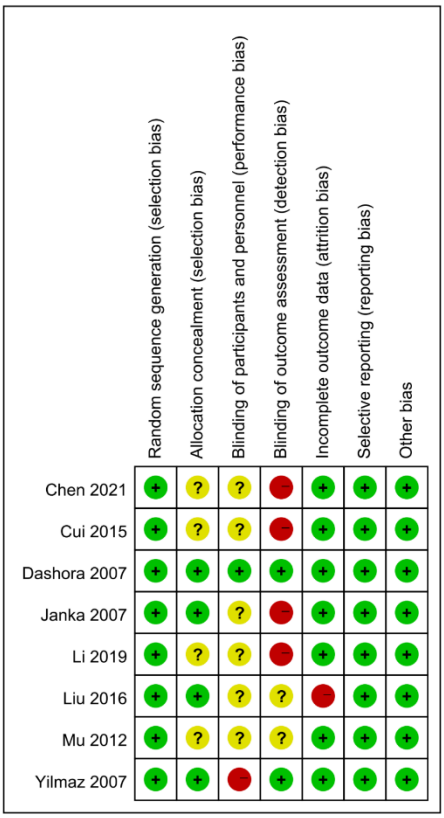

Fig. S2: Risk of bias summary

Meta-analysis results

A total of 4 studies (8,10,12,17) comparing the blood glucose control rate after treatment with hypoglycemic agents combined with insulin versus the control group were included (I^2=6%), involving 183 patients in the experimental group and 195 patients in the control group. The blood glucose control rate was higher after treatment with hypoglycemic agents combined with insulin, indicating that the combination of hypoglycemic agents and insulin had a better blood glucose control effect [RR=1.30, 95%CI (1.14,1.50), *P*=0.0001] (Fig. 2). The publication bias test found that all literature was within the funnel, indicating no publication bias (Fig. S3).

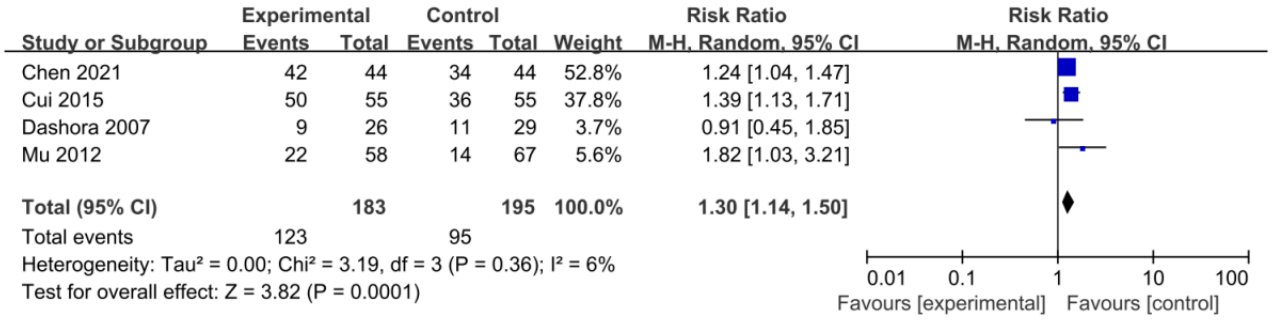

Fig. 2: Forest plot for comparison of glycaemic control rates

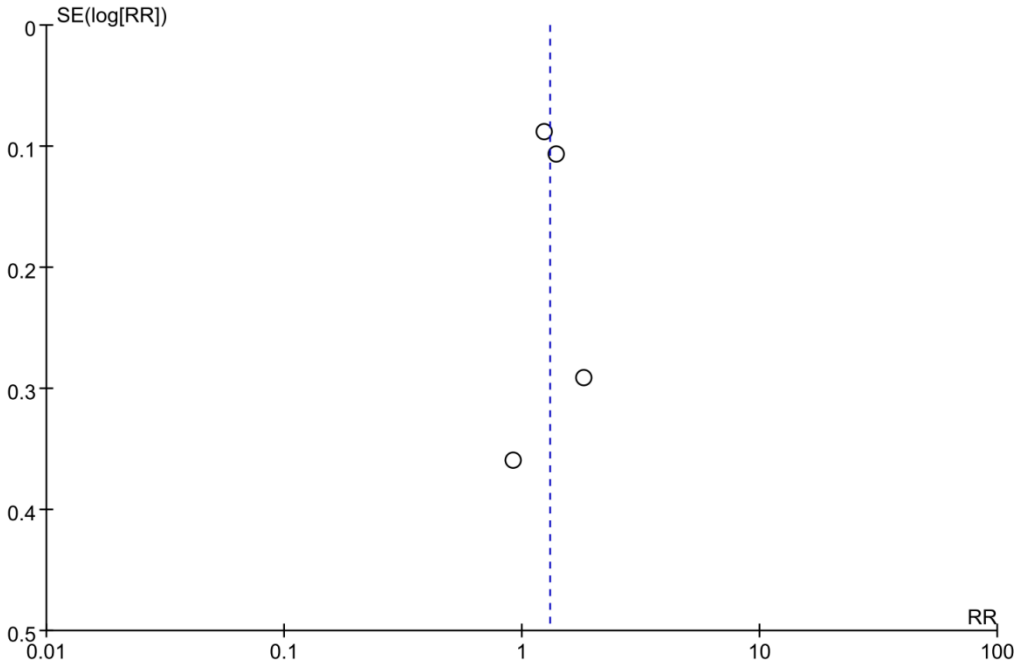

Fig. S3: Funnel plot for comparison of blood glucose control rates

Fasting blood glucose

Seven studies (9,10,12-15,17) comparing fasting blood glucose after treatment with hypoglycemic agents combined with insulin versus the control group were included (I^2=77%), involving 361 patients in the experimental group and 370 patients in the control group. The reduction in fasting blood glucose was more significant after treatment with hypoglycemic agents combined with insulin, indicating that the combination of hypoglycemic agents and insulin had a better blood glucose-lowering effect [SMD=-0.82, 95%CI (-1.14,-0.49), $P<0.00001$] (Fig. 3). The publication bias test found that the literature was symmetric on both sides of the funnel, suggesting no publication bias (Fig. S4).

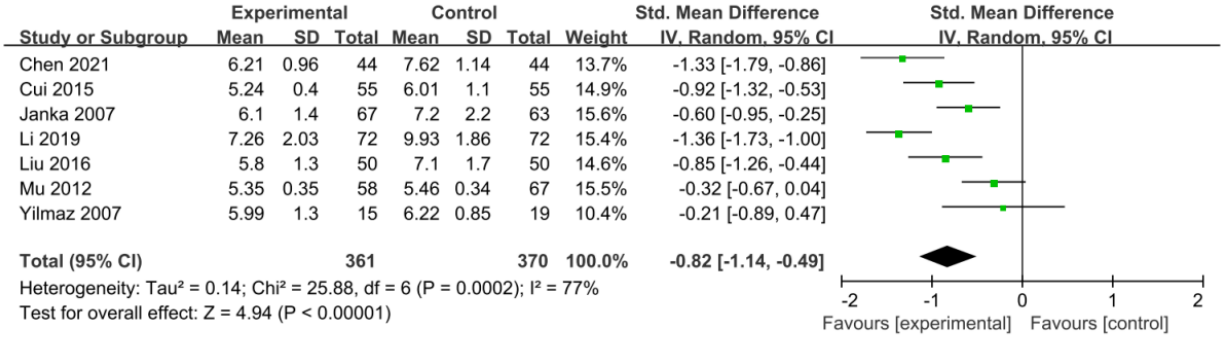

Fig. 3: Forest plot for comparison of fasting blood glucose

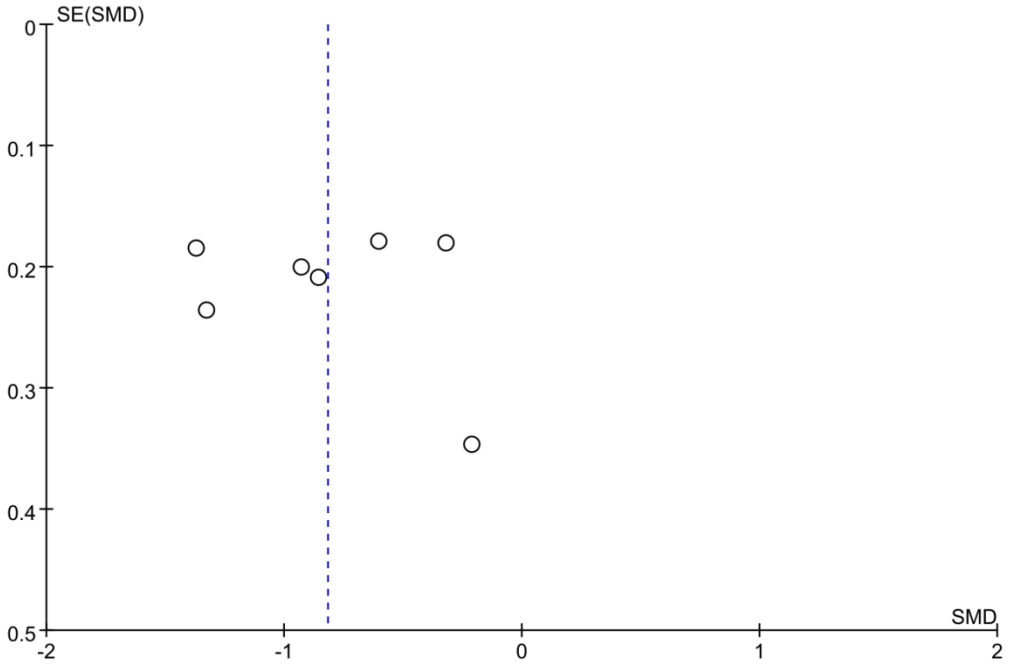

Fig. S4: Funnel plot of fasting blood glucose comparison

Postprandial 2-hour blood glucose

Six studies (10,12-15,17) comparing postprandial 2-hour blood glucose after treatment with hypoglycemic agents combined with insulin versus the control group were included (I^2=96%), involving 294 patients in the experimental group and 307 patients in the control group. The reduction in postprandial 2-hour blood glucose was more significant after treatment with hypoglycemic agents combined with insulin, indicating that the combination of hypoglycemic agents and insulin had a better blood glucose-lowering effect [SMD=-1.33, 95%CI (-2.15, -0.51), *P*=0.002] (Fig. 4). The publication bias test found that the literature symmetry is poor, suggesting that there may be publication bias in the included literature (Fig. S5).

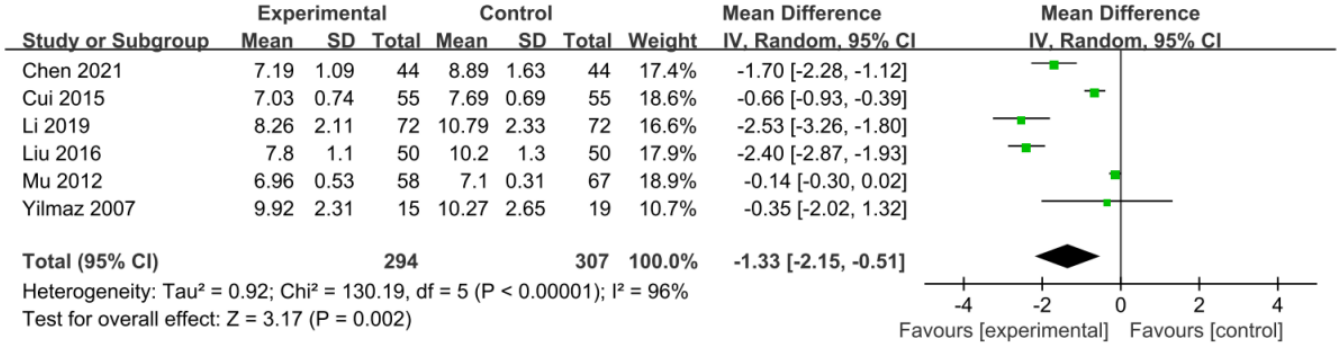

Fig. 4: Forest plot for comparison of blood glucose at 2 hours postprandial

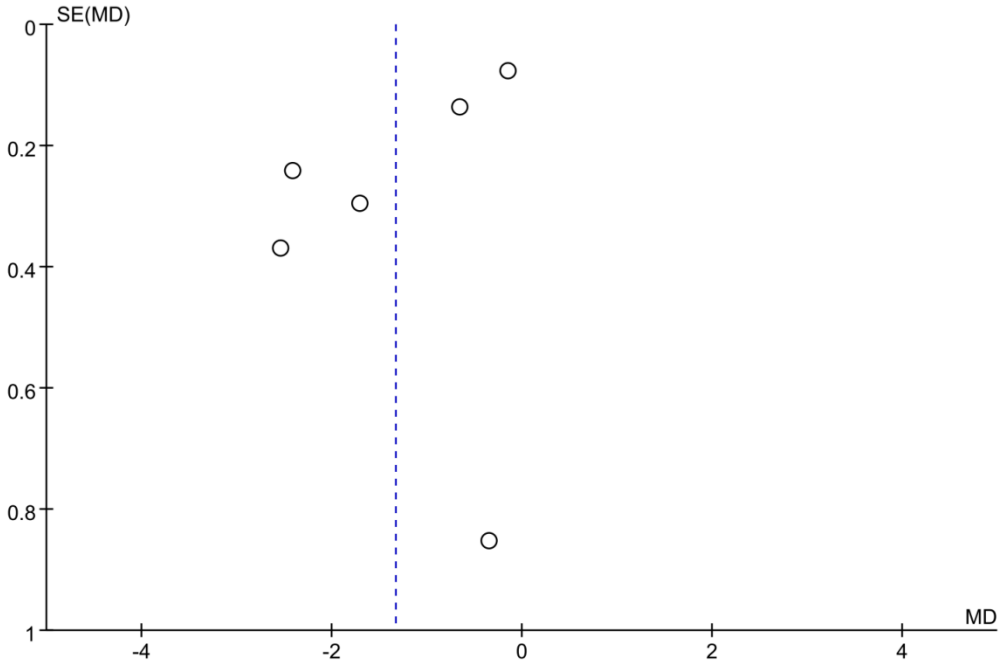

Fig. S5: Funnel plot of blood glucose comparison at 2 hours after a meal

HbA1c

Eight studies (8-10,12-15,17) comparing HbA1c after treatment with hypoglycemic agents combined with insulin versus the control group were included (I^2=95%), involving 387 patients in the experimental group and 399 patients in the control group. The reduction in HbA1c was more significant after treatment with hypoglycemic agents combined with insulin, indicating that the combination of hypoglycemic agents and insulin had a better blood glucose-lowering effect [SMD=-1.01, 95%CI (-1.71, -0.31), *P*=0.005], as shown in Fig. 5. The publication bias test found that the literature symmetry was good, suggesting that there was no publication bias in the included literature (Fig. S6).

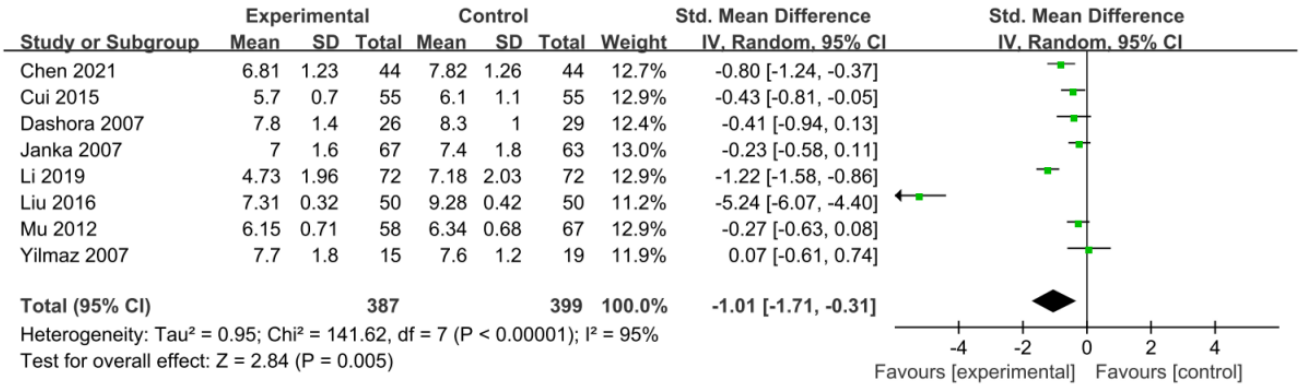

Fig. 5: Forest plot for HbA1c comparison

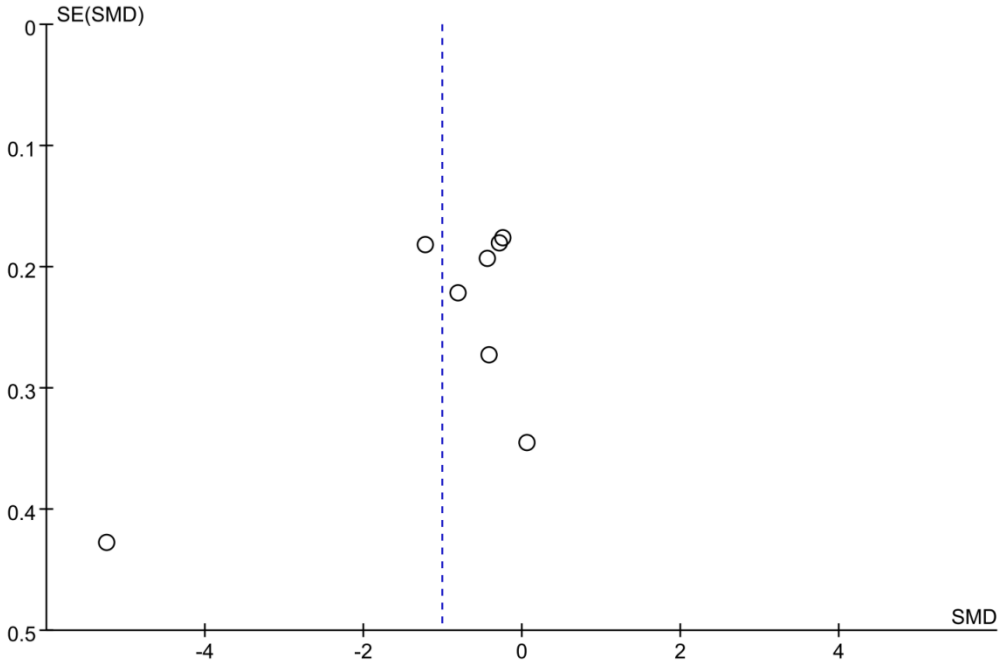

Fig. S6: Funnel plot of HbA1c comparison

Incidence of adverse reactions

Seven studies (8,9,10,12,13,15,17) comparing the incidence of adverse reactions after treatment with hypoglycemic agents combined with insulin versus the control group were included (I^2=59%), involving 372 patients in the experimental group and 380 patients in the control group. There was no difference in the incidence of adverse reactions between the patients treated with hypoglycemic agents combined with insulin and the control group [RR=0.63, 95%CI (0.36,1.07), *P*=0.09], as shown in Fig. 6. The publication bias test found that the literature symmetry was good, suggesting that there was no publication bias in the included literature (Fig. S7).

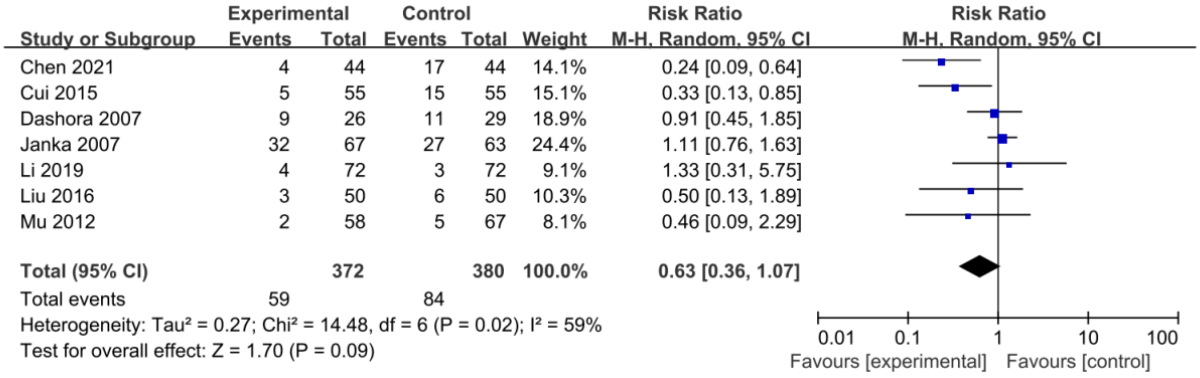

Fig. 6: Forest plot for comparison of incidence of adverse reactions

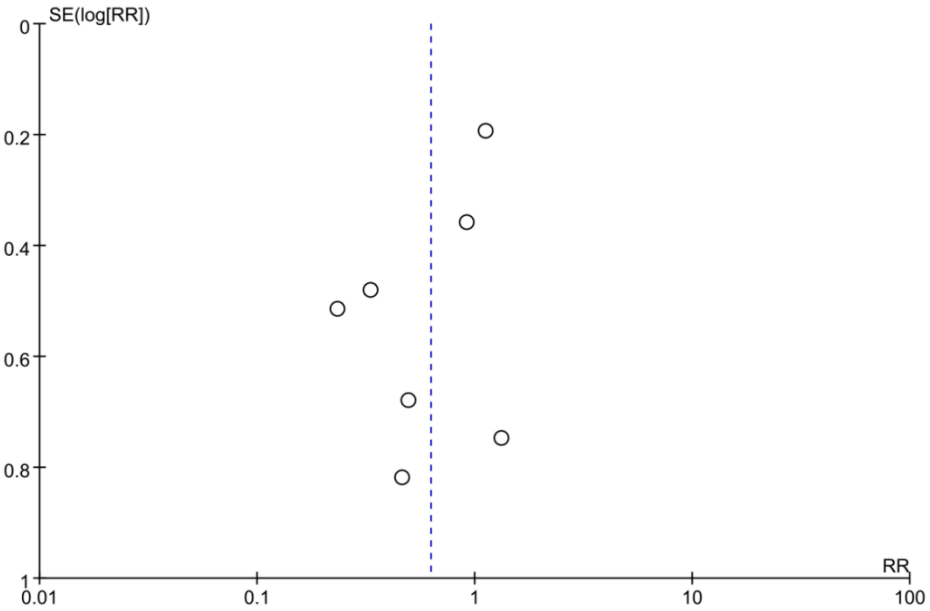

Fig. S7: Funnel plot comparing the incidence of adverse reactions

Discussion

In recent years, diabetes has gradually become a serious factor affecting patients' health, especially in middle-aged and elderly people with various underlying diseases. Poor blood glucose control can affect vital organs, aggravate the condition of diabetic patients, and even endanger their lives. In this study, we defined the lower age limit for "middle-aged and elderly" as 50 years. This threshold is based on considerations of early physiological changes, as patients may begin to exhibit age-related abnormalities in glucose metabolism during this period (2,6,19).

This study conducted a meta-analysis to compare the efficacy and safety of insulin alone versus combined use of hypoglycemic drugs and insulin on the treatment of middle-aged and elderly patients with diabetes.

The results showed that compared with insulin alone, the combination therapy significantly improved blood glucose control, reducing fasting blood glucose, 2 hours postprandial blood glucose, and HbA1c levels. These findings highlight the advantages of combination therapy in improving blood glucose control. Compared with previous studies, the results of this paper support the effectiveness of the combined use of hypoglycemic drugs and insulin in improving the therapeutic effect, which is consistent with the conclusions reported in some literatures (12, 13, 17).

At the same time, this study found that the combination was not found to increase the risk of adverse effects. The previous study indicated that combination therapy might not improve treatment outcomes or even increase the risk of adverse reactions (10). The differences may result from the study population and regional variations.

However, some studies believe that the combined use of the two drugs cannot improve the treatment effect and may even cause some adverse reactions due to the interaction between the drugs (9, 20). Another study investigated the efficacy and safety of dapagliflozin (an SGLT-2 inhibitor) combined with oral hypoglycemic agents. The results showed that the combination of dapagliflozin and oral hypoglycemic agents effectively reduced HbA1c and body weight, without increasing the incidence of hypoglycemia, although it may lead to an increased risk of urinary tract infections and genital infections (21). The efficacy improvement observed in this study may be attributed to a variety of mechanisms; first,

hypoglycemic drugs may cooperate with insulin to play a better hypoglycemic effect by improving the function of islet beta cells and enhancing tissue sensitivity to insulin. In addition, different types of hypoglycemic drugs may interact with insulin therapy through their own unique mechanisms of action to achieve optimal blood glucose control.

Limitations of this study: 1) Although we have tried our best to collect literature during the literature search, due to limited conditions, the included literature may not be comprehensive enough; 2) The sample size is relatively small, and many small-sample studies may not be included, which could potentially change the final conclusion; 3) Because the information provided in the literature is very limited. We were unable to obtain meaningful subgroup analysis results and agree that the source of heterogeneity could not be clarified; 4) The interventions in the included studies are not completely consistent during implementation, which may lead to clinical heterogeneity, and the source of some clinical heterogeneity cannot be found, which may have an impact on the conclusions. 5) There were no data on the severity of adverse reactions in the included literature, but detailed descriptive data were lacking, so we could not classify severe reactions as mild, symptomatic, asymptomatic, moderate, or severe. 6) The incomplete search strategy is one of the defects of our research. This may affect the reliability and comprehensiveness of the results. 7) This study did not carry out mechanism mining and clinical and policy research, so we could not carry out comprehensive discussion.

Conclusion

The combination of hypoglycemic agents and insulin treatment for diabetes in middle-aged and elderly patients has better efficacy and does not increase adverse reactions. The findings of this study have potential value in guiding the clinical treatment of middle-aged and elderly patients with diabetes, highlighting the importance of considering combination medication in the selection of treatment regimens and the need for individual evaluation of patients in actual clinical practice. In addition, these results also provide a basis for formulating relevant health policies, especially in optimizing treatment strategies and improving treatment outcomes in middle-aged and elderly patients with diabetes. Finally, given the limitations of the study, we call for future research to focus on higher quality clinical trials to validate the conclusions of this study and further explore the optimal model of combination therapy with different hypoglycemic agents and insulin.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Data availability statement

All data in relation to this study are presented in this manuscript. Supplementary files may be asked from the corresponding author.

Funding

This research has received funding by the Hainan Province Clinical Medical Center.

Conflict of Interest

The authors declare that there is no conflict of interests.

References

1. Zhang X, Wang Y, Li Y, et al (2024). Optimal obesity- and lipid-related indices for predicting type 2 diabetes in middle-aged and elderly Chinese. *Sci Rep*, 14(1):10901.
2. Holmager TLF, Lophaven SN, Mortensen LH, et al (2022). Selective migration and

mortality by economic status in Lolland-Falster, Denmark, 1992-2018. *Sci Rep*,12(1):19970.
3. Zolkepli H, Widodo RT, Mahmood S, et al (2022). A Review on the Delivery of Plant-Based Antidiabetic Agents Using Nanocarriers: Current Status and Their Role in Combatting Hyperglycaemia. *Polymers (Basel)*,14 (15):2991.
4. Qiao J, Zhang Z, Ji S, et al (2022). A distinct role of STING in regulating glucose homeostasis through insulin sensitivity and insulin secretion. *Proc Natl Acad Sci U S A*, 119(7):e2101848119.
5. Kashtoh H, Baek KH (2022). Recent Updates on Phytoconstituent Alpha-Glucosidase Inhibitors: An Approach towards the Treatment of Type Two Diabetes. *Plants (Basel)*,11 (20):2722.
6. Zhang P, Chen M, Zhang H, et al (2022). Effectiveness and safety of basal insulin therapy in type 2 diabetes mellitus patients with or without metformin observed in a national cohort in China. *BMC Endocr Disord*, 22(1):26.
7. Alavudeen SS, Khobrani M, Dhanapal CK, et al (2020). Comparative evaluation of biphasic insulin with metformin and triple oral hypoglycemic agents (OHA) in type 2 diabetes patients. *Saudi Pharm J*, 28:210-214.
8. Dashora UK, Sibal L, Ashwell SG, et al (2007). Insulin glargine in combination with nateglinide in people with Type 2 diabetes: a randomized placebo-controlled trial. *Diabet Med*, 24(4):344-349.
9. Janka HU, Plewe G, Busch K (2007). Combination of oral antidiabetic agents with basal insulin versus premixed insulin alone in randomized elderly patients with type 2 diabetes mellitus. *J Am Geriatr Soc,* 55(2):182-188.
10. Mu PW, Chen YM, Lu HY, et al (2012). Effects of a combination of oral antidiabetes drugs with basal insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes. *Diabetes Metab Res Rev,* 28(3):236-240.
11. Wang Z, Wang J, Kahkoska AR, et al (2021). Developing Insulin Delivery Devices with Glucose Responsiveness. *Trends Pharmacol Sci,* 42(1):31-44.
12. CUI JP, WU YX (2015). Efficacy of glargine insulin combined with oral hypoglycemic agents in the treatment of type 2 diabetes mellitus in the elderly. *China Pharmaceutical Guide,* 13(27):95-96. (in Chinese)
13. LIU FP (2016). Efficacy of glargine insulin combined with oral hypoglycemic agents in the treatment of type 2 diabetes mellitus in the elderly. *Journal of Huaihai Medicine,* 34(2):219-220. (In Chinese)
14. Yilmaz H, Gursoy A, Sahin M, et al (2007). Comparison of insulin monotherapy and combination therapy with insulin and metformin or insulin and rosiglitazone or insulin and acarbose in type 2 diabetes. *Acta Diabetol*, 44(4):187-192.
15. Li J, Ji J, Liu F, et al (2019). Insulin Glargine and Acarbose in the treatment of elderly patients with diabetes. *Pak J Med Sci,* 35(3):609-613.
16. Billings LK, Doshi A, Gouet D, et al (2018). Efficacy and Safety of IDegLira Versus Basal-Bolus Insulin Therapy in Patients With Type 2 Diabetes Uncontrolled on Metformin and Basal Insulin: The DUAL VII Randomized Clinical Trial. *Diabetes Care*, 41(5):1009-1016.
17. Chen X (2021). Effect of oral hypoglycemic drugs combined with glargine insulin in the treatment of outpatients with type 2 diabetes mellitus. *China Prac Med*, 16:117-119.
18. Papa G, Fedele V, Chiavetta A, et al (2008). Therapeutic options for elderly diabetic subjects: open label, randomized clinical trial of insulin glargine added to oral antidiabetic drugs versus increased dosage of oral antidiabetic drugs. *Acta Diabetol*, 45(1):53-59.
19. Zinman B, Aroda VR, Buse JB, et al (2019). Efficacy, Safety, and Tolerability of Oral

Semaglutide Versus Placebo Added to Insulin With or Without Metformin in Patients With Type 2 Diabetes: The PIONEER 8 Trial. *Diabetes Care*,42(12):2262-2271.

20. Yang Q, Lang Y, Yang W, et al (2023). Efficacy and safety of drugs for people with type 2 diabetes mellitus and chronic kidney disease on kidney and cardiovascular outcomes: a systematic review and network meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract*, 198:110592.
21. Xu X, Xu W, Zhuo Q, et al (2022). The efficacy and safety of dapagliflozin combined with oral hypoglycemic agents in patients with type 2 diabetes: a systematic review and meta-analysis. *Ann Palliat Med,* 11(3):1028-1037.