

Impact of Fixed Combination of Metformin and Pioglitazone on Insulin Resistance of Patients with Type 2 Diabetes: Results of a Randomized Open-Label Study

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Aim: To compare the effect of metformin, a fixed combination of metformin and pioglitazone, or dapagliflozin on insulin resistance in patients with newly diagnosed type 2 diabetes.

Methods: In this 6-week randomized open-label trial, 58 patients were randomly assigned to insulin with metformin, a fixed combination of metformin and pioglitazone, or dapagliflozin for 4 weeks. Hyperinsulinemic euglycemic clamp tests and FreeStyle Libre Pro Sensor were used to evaluate the insulin sensitivity represented by glucose-infusion rate (M value) and glycemic control, respectively. The main outcome was changes in insulin resistance compared with baseline.

Results: The baseline characteristics were well matched among the three groups. When compared to baseline, insulin sensitivity after treatment was significantly improved. Further study revealed that the fixed combination of metformin and pioglitazone provided superior M-value improvement compared with metformin, but not different from dapagliflozin. Moreover, a greater reduction in insulin dose was observed in the fixed combination of metformin and pioglitazone group than the metformin or dapagliflozin group. However, there were no significant differences in the parameters of glycemic control within the groups.

Conclusion: In patients with newly diagnosed type 2 diabetes, a fixed combination of metformin and pioglitazone provided greater improvement in insulin resistance than metformin alone and similar changes in insulin resistance to dapagliflozin.

Keywords: insulin resistance, metformin, pioglitazone, dapagliflozin, type 2 diabetes

Introduction

Type 2 diabetes mellitus (T2DM), accounting for >90% of patients with diabetes, is a chronic disease characterized by insulin resistance or relative insulin deficiency. Previous epidemiological studies have revealed that the global prevalence of T2DM has significantly increased over the last 4 decades.¹ Subjects with diabetes are susceptible to both microvascular and macrovascular complications, which lead to a long-term health damage and enormous economic losses.² Massive studies have uncovered the fundamental pathophysiological mechanisms of insulin resistance underlying the development of T2DM. Insulin resistance is a complex condition where insulin-dependent cells, such as skeletal muscle cells and adipocytes, respond inappropriately to normal insulin levels, and thus more insulin is needed to maintain normal function.³ Obesity and visceral adiposity are common habitual factors aggravating insulin resistance.⁴ Progression of insulin resistance worsens the burden on beta cells and contributes to hyperinsulinemia and frank diabetes.⁵ Moreover, insulin resistance has been demonstrated to be associated with an increased risk of cardiovascular events in patients with diabetes. Therefore, insulin resistance should be ameliorated early for the optimal management of T2DM.⁶

Among the oral antihyperglycemic drugs, metformin is effective, safe, and inexpensive, as well as able to reduce the risk of cardiovascular events and death. It may reduce fasting and postprandial plasma glucose levels by decreasing

hepatic glucose output, suppressing intestinal absorption of glucose and enhancing insulin sensitivity due to improved peripheral glucose utilization.⁷ Pioglitazone, a PPAR γ agonist, has been approved to treat T2DM for more than 20 years.⁸ Activation of PPAR γ may promote transcription of numerous genes in target organs and remodeling of white adipose tissue, which leads to an improvement in insulin sensitivity.⁹ In comparison with metformin, pioglitazone has a stronger capacity to ameliorate insulin resistance and a unique effect on insulin-mediated glucose uptake.^{10,11} Recent studies further demonstrated that pioglitazone is the first agent to prevent both progression to diabetes and major cerebrovascular diseases.¹² Clinically, both metformin and pioglitazone can be used in monotherapy or combination therapy. Greater efficacy has been obtained in combination therapy due to the different effects of metformin and pioglitazone.¹³ Moreover, a fixed-dose combination of metformin and pioglitazone provides an effective method for raising the therapeutic compliance of patients on the basis of glycemic control. SGLT2 inhibitors, a relatively new type of oral antidiabetic drug that includes dapagliflozin and empagliflozin, not only diminish reabsorption of glucose in the renal proximal tubule through inhibition of SGLT2 but also indirectly enhance peripheral insulin sensitivity owing to weight loss and elimination of glucose toxicity.¹⁴ Additionally, inhibition of SGLT2 has been demonstrated to restore brain insulin action and whole-body metabolism in individuals with prediabetes and obese rats.^{15,16}

Although the aforementioned drugs are promising treatment strategies for insulin resistance, a critical question arises as to which drug benefits patients with T2DM more from reduced insulin resistance and consequent glycemic control. In this study, we aimed to evaluate the effects of metformin, a fixed-dose combination of metformin and pioglitazone (500 mg metformin plus 15 mg pioglitazone), and dapagliflozin on insulin sensitivity and glycemic control in overweight patients with newly diagnosed T2DM.

Methods

Study Participants

The current randomized, open-label study was conducted in Nanjing First Hospital between May 2021 and February 2023. All authors of this paper participated in the recruitment of subjects. Overweight adult patients with newly diagnosed T2DM according to WHO diagnostic criteria (1999) who had received no medication for diabetes were enrolled in this study. Briefly, the inclusion criteria were willingness to participate in this study, age 18–60 years, regular diet and exercise, body mass index (BMI) ≥ 24 kg/m² and glycated hemoglobin (HbA_{1c}) $> 9\%$. Exclusion criteria were other types of diabetes, insulin allergy or intolerance of metformin, pioglitazone, or dapagliflozin, renal dysfunction (estimated glomerular filtration rate < 45 mL/(min/1.73 cm²), severe liver disease or elevated transaminases (2.5-fold the upper limit), history of alcohol dependence or drug abuse in the last 5 years, systemic steroid therapy or other medication influencing cholesterol metabolism in the last 3 months, acute infection or stress state within 1 month prior to the study, pregnancy or lactation, history of diabetic ketoacidosis within the previous year, psychiatric disease, and other serious comorbid conditions, including severe cardiovascular and pulmonary disease, heart failure of New York Heart Association class IV, and tumors. This study was approved by the research ethics board of Nanjing First Hospital, Nanjing Medical University in accordance with the Helsinki Declaration (KY20220314-01) and is registered at ClinicalTrials.gov (identifier NCT05591235). Written informed consent was obtained from all enrolled patients.

Study Design

Prior to randomization, subjects underwent eligibility screening and entered a 1-week run-in period of single insulin therapy with continuous subcutaneous insulin infusion to attain the glycemic target of fasting glucose < 7 mmol/L, 2-hour postprandial glucose < 11 mmol/L and time in range (TIR) (3.9–10 mmol/L) $\geq 80\%$ based on 7-point self-monitored blood glucose.¹⁷ Then, insulin sensitivity was evaluated using the hyperinsulinemic euglycemic clamp test. Randomization was subsequently performed by random allocation in a 1:1:1 manner using a computer-based system into three groups: group A for insulin with metformin (a minimum daily dose of 1500 mg), group B for insulin with fixed-dose combination of metformin and pioglitazone (two tablets of 500 mg metformin plus 15 mg pioglitazone), and group C for insulin with dapagliflozin (10 mg **once a day**). During this 4-week time frame, all patients were instructed to change the insulin pump infusion site and provide one profile of 7-point self-monitored blood glucose every 3 days. The insulin doses were titrated

every day by physicians to achieve glycemic control. Participants who failed to attain the glycemic target three consecutive times or could not afford the side effects of hypoglycemic medications were excluded from this study. On the last day of week 4, a FreeStyle Libre Pro Sensor (flash continuous glucose monitoring [FGM] system) was inserted to record glycemic data for up to 14 days. At the end of week 5, all antidiabetic agents were stopped and the hyperinsulinemic euglycemic clamp test was performed again for remaining subjects. This study was completed when the FGM system was removed (Figure 1A).

The sample size required was calculated using PASS 21.0.3 (NCSS, Kaysville, Utah, USA). Based on our preliminary experiment, the mean M-values were 5.8, 7.0, and 6.6 for the metformin, fixed-dose combination of metformin and pioglitazone, and dapagliflozin groups, respectively, and the standard deviation was 1.0, 0.95, and 0.9 for the three

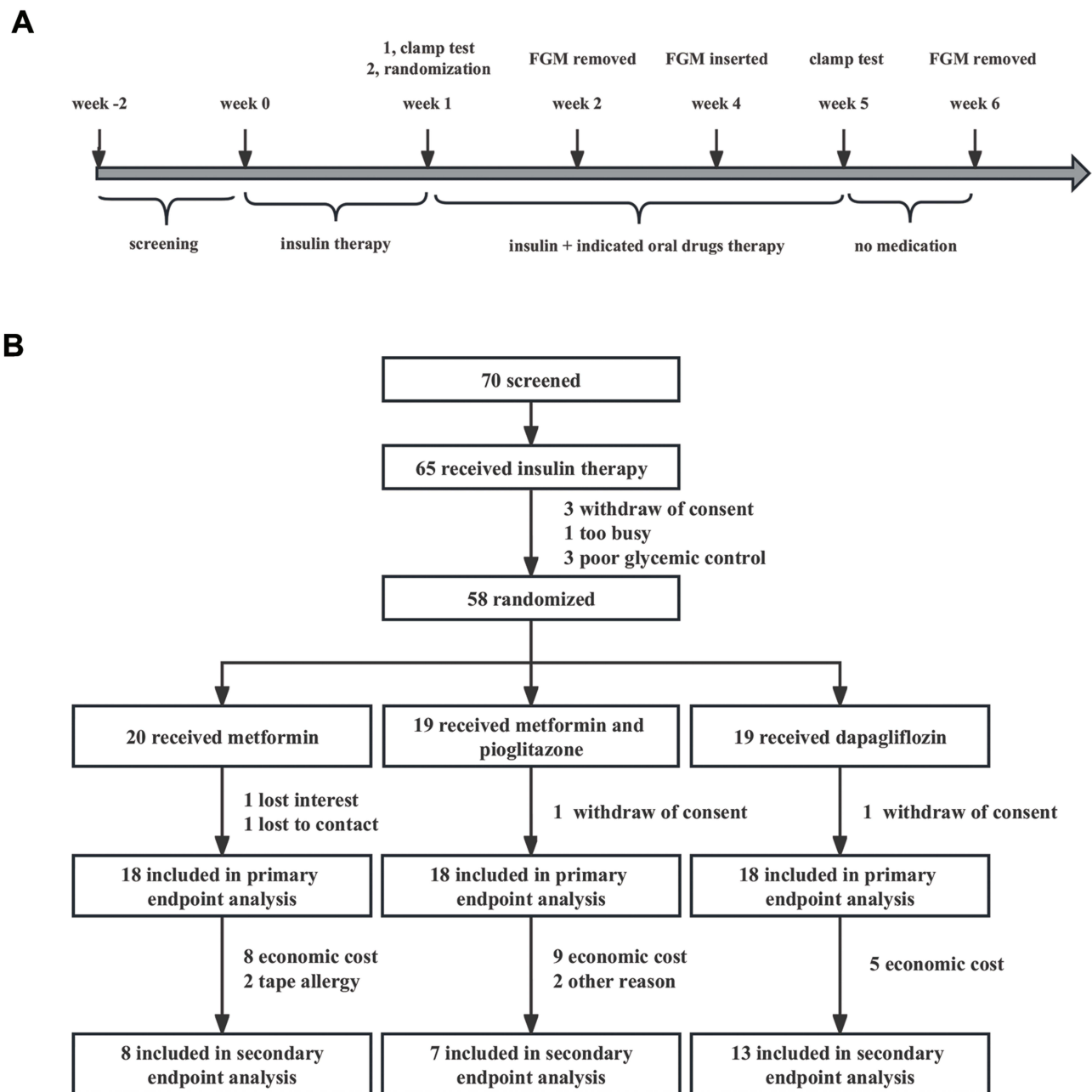


Figure 1 Study design (A) and participant flow (B).

groups, respectively. When we set the significance level (α) to 0.05 and the desired power of the study ($1 - \beta$) to 90%, the minimum number of patients required was 54. Assuming a 20% dropout rate, at least 69 cases needed to be screened.

Hyperinsulinemic Euglycemic Clamp Test

The insulin pump was stopped for 12 hours, and then the hyperinsulinemic euglycemic clamp test was performed according to a published protocol with slight adjustment.^{18,19} After 12-hour overnight fasting, exogenous primed regular human insulin was infused at a rate of 4 mU/(kg/min) for the first 10 minutes, followed by a continuous insulin infusion at 2 mU/(kg/min) for the remaining 140 minutes in order to totally inhibit endogenous glucose production. The glucose-infusion rate was adjusted to achieve the target glucose level (4.5–5.5 mmol/L) based on the blood glucose measured every 5 minutes. The steady glucose-infusion rate during the last 30 minutes (120–150 min) was used to calculate the glucose-metabolized (M) value (mg/[kg/min]).

Measurements

Demographic data (name, age, and sex) and anthropometric measures (weight, height, and blood pressure) were collected at baseline and the end of study if needed. Fasting venous blood samples were drawn for laboratory measurements. Conventional routine methods were used for determination of fasting glucose and lipid profiles. Serum HbA_{1c} and C-peptide were measured by high-performance liquid chromatography and radioimmunoassay, respectively.

End Points

The primary end point was changes in insulin resistance represented by M value from week 1 to week 5. Additionally, insulin doses and body weight were evaluated over the same time period for the primary end point. Secondary end points were glycemic control assessed by FGM, including TIR, mean glucose level, and mean amplitude of glycemic excursions between week 4 and week 6. All safety end points, including diabetic ketoacidosis, metabolic acidosis, heart failure or myocardial infarction, urinary tract infection, edema, cancer, and death, were also documented throughout this study.

Statistical Analysis

All analyses were performed with SPSS 20 (IBM, USA). Normally distributed continuous variables are presented as means \pm SD and skewed data as medians (IQR) or as indicated. Categorical variables are given as numbers and percentages. Differences among three groups were assessed using one-way ANOVA (normally distributed variables), Kruskal–Wallis H test (skewed variables), or χ^2 test (categorical variables) as appropriate. ANCOVA was used for the analysis of changes in M values, insulin dose, and body weight from baseline to week 5. Two-sided $P < 0.05$ was considered statistically significant.

Results

Participant Disposition

A total of 70 subjects were screened, and 65 consented to participate in the study. Of the 58 participants who completed the therapy, 20 were randomized to the metformin group, 19 to the fixed-dose combination of metformin and pioglitazone group, and 19 to the dapagliflozin group. Dropout rates at the end of this study were 10.0% (two of 20), 5.2% (one of 19), and 5.2% (one of 19) in the metformin group, fixed-dose combination of metformin and pioglitazone group, and the dapagliflozin group, respectively. Detailed reasons for dropouts are shown in [Figure 1B](#).

Baseline Characteristics

As shown in [Table 1](#), age, sex, BMI and prevalence of hypertension were well matched among the three groups ($P > 0.05$). There were no differences in most of the clinical parameters either, including lipid profiles (triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol), metrics of glucose control (fasting plasma glucose and HbA_{1c}), measures of insulin secretion (C-peptide and postprandial C-peptide), and renal and liver function (glomerular

Table 1 Demographic, anthropometric, and disease characteristics of trial patients

	Metformin (n=18)	Metformin + pioglitazone (n=18)	Dapagliflozin (n=18)	P
Sex (male/female)	13/5	12/6	11/7	0.934
Hypertension (yes/no)	4/14	7/11	2/16	0.181
Age (years)	47.56±13.03	43.22±11.27	44.89±8.82	0.507
BMI (kg/m ²)	26.61±2.78	27.52±3.23	26.42±2.81	0.494
HbA _{1c} (%)	11.07±1.35	11.21±1.63	10.88±1.47	0.809
ALT (U/L)	25.00 (14.00, 36.05)	34.00 (22.85, 60.00)	24.20 (18.97, 42.75)	0.243
AST (U/L)	15.50 (9.00, 22.17)	20.50 (16.92, 23.07)	15.55 (13.00, 29.17)	0.238
TC (mmol/L)	4.84±0.87	4.80±0.87	5.79±1.95	0.050
TGs (mmol/L)	2.26±1.73	2.03±1.43	2.05±1.37	0.876
HDL-C (mmol/L)	1.10±0.32	1.10±0.21	1.14±0.16	0.836
LDL-C (mmol/L)	3.00±0.76	2.98±0.78	3.72±1.42	0.062
C-peptide (ng/mL)	1.28 (0.98, 2.04)	1.41 (0.92–2.36)	1.24 (0.61–1.79)	0.496
C-peptide 2 h (ng/mL)	3.40 (2.03, 4.88)	2.56 (1.98–4.80)	2.78 (1.08–4.20)	0.513
FPG (mmol/L)	10.13±3.34	10.24±3.45	9.55±3.54	0.812
GFR (mL/min/1.73 m ²)	119.63±41.91	138.81±43.52	121.6±32.25	0.286

Notes: Data are presented as means ± SD, medians (IQR), or numbers as appropriate. ANOVA for comparison of normally distributed data, Kruskal–Wallis *H* test for comparison of asymmetrically distributed data, and Pearson's χ^2 test for comparison of categorical variables.

Abbreviations: BMI, body mass index; HbA_{1c}, glycosylated hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TC, total cholesterol; TGs, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; GFR, glomerular filtration rate.

filtration rate, alanine transaminase, and aspartate transaminase) among groups ($P>0.05$). Higher total cholesterol in the dapagliflozin group was observed ($P<0.05$).

Primary Outcome

Insulin sensitivity improved significantly in all groups (Figure 2A), whereas absolute M values were comparable among the groups after treatment. The rise in M values with the fixed dose combination of metformin and pioglitazone was significantly greater than with metformin with adjustment for baseline M levels, but not different from dapagliflozin (Figure 2A). With the improvement in insulin sensitivity, insulin dose decreased in all groups. The fixed-dose combination of metformin and pioglitazone showed the highest reduction in insulin dose when compared with metformin and dapagliflozin (Figure 2B). However, we did not observe significant changes in body weight among the three groups (Figure 2C).

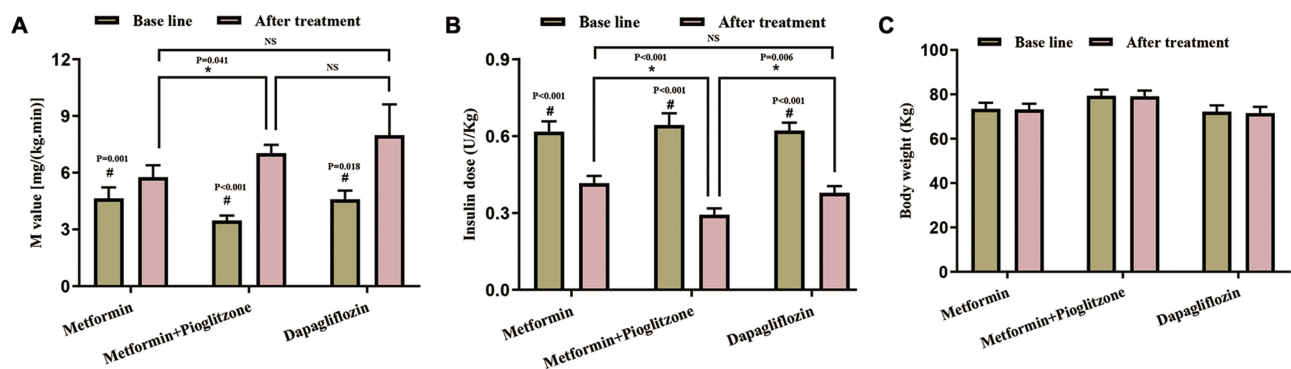


Figure 2 Changes in M value (A), insulin dose (B), and body weight (C) before and after treatment were evaluated. Data are presented as means with SEM error. * $P<0.05$ between the three groups; # $p<0.05$ within the same group.

Secondary Outcomes

As for glycemic parameters, there were no significant differences in mean glucose, TIR, time below range, time above range, low blood glucose index, high blood glucose index, or mean amplitude of glycemic excursions within the three groups with or without medication according to the FGM data ([Supplementary Table 1](#)).

Safety Outcomes

No severe adverse events were reported in the current study. Moderate gastrointestinal side effects, such as nausea, diarrhea, and reduced appetite, were observed in four subjects in the metformin group, two in the fixed-dose combination of metformin and pioglitazone group, and one in the dapagliflozin group ($P=0.317$). None of the patients suffered from heart failure, fracture, edema, or urinary tract infection.

Discussion

Therapies for insulin resistance have stagnated for a number of years due to a lack of knowledge of underlying mechanisms and specific molecular drug targets. Previous studies revealed that increased glucose–fatty acid cycle, *O*-GlcNAcylation of key enzymes in the hexosamine biosynthesis pathway, ectopic lipid accumulation, and inflammation and endoplasmic reticulum stress associated with insulin resistance.^{20,21} Therefore, stimulation of fat oxidation and muscle mass and inhibition of hepatic fat synthesis with novel molecular compounds might provide an alternative strategy for insulin resistance.

Consistently with the DEFENCE study by Shigiyama et al, insulin resistance as assessed by homeostatic model assessment of insulin resistance (HOMA-IR) decreased significantly in both dapagliflozin and metformin groups in patients with early-stage T2DM, while the improvement in insulin sensitivity was comparable between the two groups.²² In patients with T2DM receiving stable basal insulin therapy, HOMA-IR was improved with an add-on therapy in combination with pioglitazone and metformin other than metformin alone.²³ There have also been studies demonstrating that pioglitazone–metformin combination therapy is associated with significantly decreased levels of HOMA-IR when compared with metformin monotherapy in patients with T2DM.^{13,24} In contrast, HOMA-IR did not change consistently with dapagliflozin or metformin treatment in a population of overweight women with gestational diabetes pregnancy.²⁵ Several factors may contribute to the inconsistency in these findings, including different disease populations, ethnicity, and sample size. Furthermore, the hyperinsulinemic euglycemic clamp test, the gold-standard method for assessing insulin sensitivity, was performed in this study, which varies from the aforementioned studies.

Among the currently available antidiabetic agents, dapagliflozin exerts hypoglycemic effects independently of insulin secretion and insulin resistance, which significantly decreases **HbA_{1c}** and BMI when compared with placebo. Monotherapy with dapagliflozin displays a similar reduction in **HbA_{1c}** and fasting blood glucose with metformin or pioglitazone.²⁶ Given the unique protective effect on macrovascular and renal complications, dapagliflozin is a preferred choice in patients with atherosclerotic cardiovascular disease, heart failure, or moderate chronic kidney disease.²⁷ However, concerns about the risk of lower-limb amputation, euglycemic ketoacidosis, bone fracture, acute renal injury, and Fournier gangrene have also been raised with the extensive application of dapagliflozin.²⁸ Dapagliflozin should be prescribed with caution after balancing the benefits with side effects. Although the indirect insulin-sensitizing action of dapagliflozin mainly relies on the relief of glucose toxicity,²⁸ we observed improved insulin sensitivity with dapagliflozin under tight glycemic control, which indicated a direct role of dapagliflozin in insulin resistance. Possibly, dapagliflozin may exert beneficial roles in insulin sensitivity through attenuating the downregulation of pAkt and increasing GLUT4 protein levels.^{29,30} Dapagliflozin administration can also decrease the expression level of oxidative stress markers and suppress the secretion of inflammatory cytokines, both of which may improve insulin resistance.^{31,32} Furthermore, the insulin resistance–lowering effect of dapagliflozin could partly be explained by enhancing fat utilization and browning of adipose tissue, thus inhibiting fat accumulation and hepatic steatosis.³³

In comparison with dapagliflozin, pioglitazone is a powerful insulin sensitizer that directly improves insulin sensitivity through activating insulin signaling on muscle cells.³⁴ Although pioglitazone remains available at an accessible price in clinical management, its usage has dramatically declined due to the fear of side effects. It has long been blamed for increased risk of bladder cancer and atypical bone fractures.³⁵ Fluid retention caused by

pioglitazone has also restricted its application in patients with congestive heart failure. However, there are several unique advantages of pioglitazone, such as durable responsiveness, reasonable price, low risk of hypoglycemia as monotherapy, flexible combination with additional agents, and little influence of renal function.³⁶ In patients with prediabetes, pioglitazone treatment may delay the development of T2DM with sparse serious adverse events and cardiovascular complications, according to a recent meta-analysis of 4186 participants.³⁷ Emerging evidence has also demonstrated the protective effect of a low dose of pioglitazone on liver steatosis and inflammation independent of glycemic control in patients with T2DM.³⁸ Moreover, pioglitazone can reduce the risk of myocardial infarction and ischemic stroke in primary and secondary prevention without proven direct harm on the myocardium. In vitro studies have confirmed that pioglitazone shows solid benefits on cardiomyocyte electrophysiology, ischemia–reperfusion injury, and cardiac remodeling.^{39,40} Given the beneficial effects, it might be time to reconsider the status of pioglitazone in therapeutic strategies for T2DM.

Metformin is a very modest insulin sensitizer in muscle and a powerful drug targeting glucose production in liver.⁴¹ It has been shown that metformin confers cardiovascular protection in patients with T2DM;^{42,43} however, there have been studies showing no benefits of metformin on mortality or cardiovascular risk.^{44–47} Metformin and pioglitazone improve insulin sensitivity through different molecular and organ-specific mechanisms. The synergistic action of metformin and pioglitazone provides a rationale for the combination of both drugs in treatment of insulin resistance. In addition to the benefits over glycemic control, improvements in diabetic dyslipidemia, inflammation, and cardiovascular events have been reported. Therefore, the fixed-dose combination of pioglitazone and metformin serves as a more convenient option for control of T2DM based on the bioequivalence between the fixed-dose combination and coadministration of individual medication.⁴⁸

Clinically, lean individuals with insulin resistance are not uncommon. Results from a cross-sectional study showed that half the young insulin-resistant adults were lean.⁴⁹ It was inappropriate to treat these lean but insulin-resistant subjects with metformin or dapagliflozin, which might further exacerbate weight loss. Conversely, a combination of pioglitazone and metformin may counteract adverse events without masking the significant improvement in blood glucose control, as weight gain is a well-known disadvantage of pioglitazone.^{50,51} Additionally, pioglitazone was also proved to mitigate the dapagliflozin-related weight loss.⁵² Therefore, a bright future for fixed-dose combination metformin and pioglitazone application can be seen for diabetic patients, especially those with cardiovascular complications, poor lipid control, and low body weight. The failure to find significant changes in body weight in the current study may be explained by the short time frame.

There are several strengths to our study. The gold-standard technique of the hyperinsulinemic euglycemic clamp test was applied to evaluate insulin resistance before and after antidiabetic agent treatment. To avoid the influence of hyperglycemia on insulin sensitivity,^{53,54} all included participants received a period of intensive therapy in order to maintain optimized glycemic control before assessing insulin sensitivity.

However, some limitations should be addressed. We could not ascertain the effect of long-term exposure of insulin combined with metformin, a fixed-dose combination of metformin and pioglitazone, or dapagliflozin on insulin sensitivity, glycemic control, or weight due to a short duration of intervention. Moreover, the lipid profiles and C-peptide were not reassessed at the end of the trial; therefore, whether the current treatments can improve islet secretion was unclear. Additionally, the data on glycemic control assessed by FGM may be not reliable due to too many patients dropping out. To better explore the effects on glucose fluctuation, it is undoubtedly crucial to include more data on glycemic control assessed by FGM.

In conclusion, a short-term fixed combination of metformin and pioglitazone provides better improvement in insulin sensitivity than metformin alone and similar changes in insulin resistance with dapagliflozin in overweight individuals with T2DM. Further study with a substantial sample and longer follow-up are warranted to confirm the findings.

Abbreviations

BMI, body mass index; TIR, time in range.

Data Sharing

The data are not freely publicly available due to privacy reasons. After publication, the data presented in this study will be available upon request from the corresponding author.

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Disclosure

The authors have no conflicts of interest to declare for this work.

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