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Comparative efficacy and safety of sitagliptin or gliclazide combined with metformin in treatment-naive patients with type 2 diabetes

A single-center, prospective, randomized, controlled, noninferiority study with genetic polymorphism analysis

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Abstract

Background: This study evaluates the efficacy and safety of sitagliptin versus gliclazide, combined with metformin, in treatment-naive patients with type 2 diabetes mellitus (T2DM) and glucotoxicity.

Methods: In this single-center, randomized, controlled noninferiority trial, 129 treatment-naive patients with T2DM with glucotoxicity (fasting plasma glucose [FPG] ≥ 200 mg/dL and glycated hemoglobin ≥ 9.0%) were randomized to receive sitagliptin plus metformin (n = 66) or gliclazide plus metformin (n = 63) for 12 weeks. Sitagliptin and gliclazide were given for the first 4 weeks, followed by metformin monotherapy for 8 weeks. Efficacy end points included changes in glycemic control, body weight, and β-cell function at baseline, 4 weeks, and 12 weeks.

Results: After 12 weeks, mean glycated hemoglobin reductions were 4.03% in the sitagliptin group and 4.13% in the gliclazide group, with a mean difference of –0.097 (95% confidence interval, –0.648 to 0.453), confirming noninferiority. Both groups showed significant FPG reductions at 4 weeks ($P < .05$). The sitagliptin group achieved faster glycemic targets, greater FPG and body weight reductions, and higher rates of FPG < 6.1 mmol/L (26.2% vs 5.7%; $P = .012$). No significant differences were observed in β-cell function or hypoglycemia incidence ($P > .05$). Genetic analysis showed specific single-nucleotide polymorphisms affected drug efficacy: dipeptidyl peptidase-4 rs2909451 TT and rs4664443 GG genotypes showed lower efficacy with sitagliptin, while GLP1R rs3765467 AG and KCNJ11 rs2285676 CC genotypes responded better to sitagliptin.

Conclusion: Sitagliptin combined with metformin is noninferior to gliclazide combined with metformin in treatment-naive patients with T2DM with glucotoxicity. Genetic polymorphisms significantly affect drug efficacy, highlighting the importance of personalized medicine. The sitagliptin group achieved glycemic targets more quickly and had greater weight reductions without increased adverse effects.

Abbreviations: AUC-INS = area under the curve for insulin, AUC-PG = area under the curve for plasma glucose, BMI = body mass index, CI = confidence interval, DI = disposition index, DPP-4 = dipeptidyl peptidase-4, FPG = fasting plasma glucose, GLP-1 = glucagon-like peptide-1, HbA1c = glycated hemoglobin, HOMA-IR = homeostatic model assessment of insulin resistance, HOMA-β = homeostatic model assessment of β-cell function, IQR = interquartile range, I_p/I_0 = peak insulin-to-baseline insulin ratio, MBCI = modified β-cell function index, T2DM = type 2 diabetes mellitus, $\Delta I_{60}/\Delta G_{60}$ = incremental insulin-to-glucose ratio at 60 minutes.

Keywords: gliclazide, glucotoxicity, sitagliptin, type 2 diabetes mellitus

1. Introduction

The global prevalence and incidence of diabetes are increasing rapidly. According to the International Diabetes Federation, there were 529 million people with diabetes worldwide in 2021, with an age-standardized prevalence rate of 6.1%. By 2050, it is projected that there will be 1.31 billion people with diabetes

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The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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globally, with global healthcare expenditures for diabetes reaching $727 billion.[1]

Recent epidemiological surveys in China indicate that the prevalence of diabetes in the country is as high as 10.9%, with an awareness rate among patients of only 36.5% and a control rate of merely 49.2%.[2] The rapid increase in the number of patients with diabetes, coupled with low control rates, underscores the urgent need for more effective treatment strategies.

Patients with significant glucotoxicity, characterized by severe hyperglycemia, represent a particularly challenging subgroup due to their accelerated β-cell dysfunction and increased risk of diabetes-related complications. Chronic hyperglycemia leads to nonphysiological and irreversible damage to pancreatic β cells, inhibiting their secretory function and accelerating β-cell failure. Primary international clinical practice guidelines[3,4] recommend short-term intensive insulin therapy for treatment-naive patients with type 2 diabetes mellitus (T2DM) who have significant hyperglycemia symptoms. However, initiating insulin therapy in treatment-naive patients with T2DM can be challenging. In contrast, oral hypoglycemic agents are more straightforward to administer and more feasible for patients. Nonetheless, evidence supporting the use of oral agents in glucotoxic patients is limited, highlighting the need for further investigation.

Dipeptidyl peptidase-4 (DPP-4) inhibitors reduce the inactivation of glucagon-like peptide-1 (GLP-1) by inhibiting DPP-4 activity, thereby increasing active GLP-1 levels within physiological ranges. This enhances glucose-dependent insulin release and reduces glucagon levels.[5] Gliclazide, a sulfonylurea, rapidly stimulates insulin secretion by binding to the sulfonylurea receptor subunit on pancreatic β cells, closing ATP-dependent potassium channels,[6] and is recommended by various clinical practice guidelines.[4,7]

The selection of oral hypoglycemic agents for treatment-naive patients with T2DM with glucotoxicity is a subject of debate in various countries, including China and other developing countries, due to factors such as drug availability, pharmacoeconomics, and government healthcare policies. Metformin, a biguanide derivative, is commonly recommended as a preferred oral hypoglycemic agent for managing T2DM.[8,9] While international guidelines often recommend metformin and lifestyle modifications for newly diagnosed T2DM, variations arise in the choice of second- and third-line oral hypoglycemic agents.[10] Studies have investigated the efficacy of different oral hypoglycemic agents in T2DM management. For example, herbal decoctions such as modified Gangsimtang have demonstrated hypoglycemic effects in patients with severe T2DM.[11] In addition, research has explored the remission effect of canagliflozin and the potential benefits of *Bifidobacterium longum* WHH2270 in improving T2DM symptoms.[12,13] Furthermore, the use of empagliflozin, a sodium-glucose cotransporter-2 inhibitor, has shown improvements in glycemic control and weight loss in patients with T2DM.[13,14] Various studies have compared the effectiveness and safety of different oral hypoglycemic agents, such as metformin, sitagliptin, and quadruple oral hypoglycemic agents, in T2DM management.[15] Moreover, research has explored the impact of these agents on factors such as liver fat, microalbuminuria, and dyslipidemia in patients with T2DM.[16,17] Investigations have also delved into the potential of novel treatments such as δ-tocotrienol supplementation and Jin-Gui Shen-Qi Wan in managing T2DM. Understanding the implications of various oral hypoglycemic agents and their effects on glycemic control, diabetic complications, medication adherence, and patient outcomes is essential for optimizing T2DM management strategies in diverse healthcare settings. This study focuses on treatment-naive patients with T2DM with glucotoxicity (HbA1c ≥ 9.0% and FPG ≥ 11.1 mmol/L) to evaluate the efficacy and safety of sitagliptin combined with metformin versus gliclazide. The study aims to assess the impact on β-cell function and insulin resistance, providing a safe, effective, and convenient treatment option for treatment-naive patients with T2DM with glucotoxicity.

2. Methods

2.1. Study design and participants

This single-center, prospective, randomized, controlled, non-inferiority study, which is of utmost importance, included treatment-naive patients with T2DM. Participants were recruited from Nanfang Hospital of Southern Medical University between September 1, 2023, and March 1, 2024. The study protocol, which was meticulously reviewed and approved by the esteemed Ethics Committee of Nanfang Hospital of Southern Medical University (ethics approval no. XL20230031), is a testament to the crucial role played by the committee in ensuring the ethical conduct of clinical research. Written informed consent was obtained from all participants prior to enrollment. Eligible subjects were randomized into the intervention or control group using a random number table, with the sequence generated by an independent third party and concealed in opaque envelopes.

The inclusion criteria are given as follows: demonstrably understand the study objectives with voluntary participation, documented by signed informed consent; newly diagnosed, treatment-naive individuals with T2DM; the age range is between 18 and 70 years, with a body mass index (BMI) ranging from 18 to 30 kg/m^2; normal hepatic and renal function, defined as alanine aminotransferase and aspartate aminotransferase levels not exceeding 2.5× the upper limit of normal, serum creatinine within normal limits, and urine ketone bodies not exceeding (1+); fasting plasma glucose (FPG) levels ≥ 200 mg/dL (11.1 mmol/L) and glycated hemoglobin (HbA1c) ≥ 9.0%; and capability to adhere to the prescribed antidiabetic regimen, follow dietary guidelines, and self-monitor fasting and postprandial blood glucose levels.

Exclusion criteria included the following: a diagnosis of type 1 diabetes mellitus; hepatic or renal dysfunction indicated by serum creatinine levels above 1.2× the upper limit of normal; previous use of hypoglycemic medications before screening; a history of severe ketosis, ketoacidosis, or hyperosmolar hyperglycemic state; ongoing treatment with corticosteroids, immunosuppressive agents, or cytotoxic drugs or a history of pancreatitis or pancreatic surgery; major systemic diseases such as cardiovascular, respiratory, gastrointestinal, neurological, endocrine, or genitourinary disorders, severe anemia, malignancies, psychiatric disorders, or other conditions likely to interfere with study results; pregnant or breastfeeding women; known allergies to sitagliptin or gliclazide; and poor compliance potential as assessed by the investigator, which may preclude completion of study requirements.

2.2. Intervention measures and follow-up protocol

In the intervention arm, participants were administered sitagliptin phosphate (100 mg daily, manufactured by Merck) and metformin (500 mg 3× daily, orally manufactured by Bristol Myers Squibb) for 4 weeks. Following this phase, participants were transitioned to monotherapy with metformin for an additional 8 weeks. Conversely, the control group received gliclazide MR (2 mg daily, orally, manufactured by Sanofi) combined with metformin (500 mg 3× daily, orally, manufactured by Bristol Myers Squibb) for 4 weeks, after which they too were transitioned to monotherapy with metformin for 8 weeks.

The initial follow-up visit was conducted with utmost regularity prior to study initiation to screen eligible patients with T2DM. Subsequent to screening, those meeting the inclusion criteria commenced pharmacological treatment at the second follow-up, thereby marking the beginning of the study. This was followed by a treatment period extending over twelve weeks. Additional follow-up assessments were scheduled with

consistent regularity at weeks 2, 4, 8, and 12, during which patients were contacted weekly via telephone to document occurrences and timings of hypoglycemic events and blood glucose control and to record all adverse events, whether related or unrelated to the study medications. The adjudication of adverse events in relation to the study protocol was performed by the investigators.

The primary end point of the study was the change in HbA1c from baseline to week 12. Secondary end points included changes in FPG, body weight, and BMI over the 12-week period. In addition, the study assessed the proportions of participants who achieved specific FPG levels of <6.1 [7] and <7.2 mmol/L,[18] as well as HbA1c goals by week 12. The time required to achieve these glycemic targets was also evaluated between the 2 groups. Anthropometric measurements such as height, weight, waist circumference, and hip circumference were recorded at baseline and at each subsequent visit, with measurements accurate to 0.1 kg and 0.1 cm. These measurements were used to calculate BMI. Biochemical parameters, including serum FPG, lipid profiles, and routine urinalysis, were evaluated at baseline and at 2, 4, 8, and 12 weeks.

Throughout the 12-week follow-up period, an oral glucose tolerance test was conducted to assess glucose and insulin dynamics. Fasting insulin levels and insulin responses at 60, 120, and 180 minutes after glucose ingestion were measured. From these data, several indices were calculated, including the homeostatic model assessment of insulin resistance (HOMA-IR), homeostatic model assessment of β-cell function (HOMA-β), area under the curve for plasma glucose (AUC-PG), and area under the curve for insulin (AUC-INS). Additional indices such as the incremental insulin-to-glucose ratio at 60 minutes ($\Delta I_{60}/\Delta G_{60}$), the peak insulin-to-baseline insulin ratio (I_p/I_0), the disposition index (DI), and the modified β-cell function index (MBCI) were calculated to provide comprehensive evaluations of β-cell functionality across the study cohorts.

The specific calculation formulas are given as follows[19–21]:

- $HOMA - IR = FINS \times FPG/22.5$
- $HOMA - \beta = 20 \times FINS/(FPG - 3.5)$
- $AUG - PG = \frac{(PG_{0\ min} + PG_{60\ min})}{2} + PG_{120\ min} + PG_{180\ min}$
- $AUG - INS = \frac{(INS_{0\ min} + INS_{60\ min})}{2} + INS_{120\ min} + INS_{180\ min}$
- $\Delta I_{60}/\Delta G_{60} = \frac{(INS_{60\ min} - INS_{0\ min})}{(PG_{60\ min} - PG_{0\ min})}$
- $I_p/I_0 = Peak\ insulin/Fasting\ insulin$
- $DI = \frac{(\Delta I_{60}/\Delta G_{60})}{HOMA - IR}$
- $MBCI = \frac{(INS_{0\ min} \times PG_{0\ min})}{(PG_{120\ min} + PG_{60\ min} - 2 \times PG_{0\ min})}$.

2.3. Pharmacogenomics analysis

2.3.1. Sample collection and DNA extraction. Whole genome analysis techniques were employed to investigate the impact of genetic polymorphisms on drug efficacy and safety. At the commencement of the study, fasting venous blood samples were collected from all participants, including the study and control groups. Approximately 5 mL of blood was drawn from each participant using EDTA anticoagulant tubes (10 mL, Vacutainer, BD Medical, Franklin Lakes, NJ). Genomic DNA was extracted from the blood samples using a commercial DNA extraction kit (DP304, Tiangen Biotech, Beijing, China). The extraction process strictly followed the manufacturer's protocol, which included steps for lysis, binding, washing, and elution of the blood samples. The concentration and purity of the DNA samples were assessed using a NanoDrop spectrophotometer, ensuring an OD260/280 ratio between 1.8 and 2.0. The extracted DNA samples were stored at −20 °C until further analysis.

2.3.2. Whole genome analysis. Whole genome sequencing was performed on the extracted DNA samples using the Illumina HiSeq X Ten platform (Illumina, San Diego, CA), achieving a coverage depth of over 1000-fold per sample to ensure high-quality genomic data. Quality control of the raw sequencing data was conducted using FASTQC. Sequencing reads were aligned to the human reference genome (GRCh38) using BWA, and variant detection was performed with GATK to identify single-nucleotide polymorphisms and insertions/deletions. Functional annotation of the identified variants was conducted using ANNOVAR to determine genetic polymorphisms related to drug metabolism. Genotypes at target loci, including DPP-4, GLP1R, KCNQ1, KCNJ11, CDKAL1, CYP2C9, and CYP2C19, were ascertained for each participant.

2.3.3. Genotype analysis. Sequencing results were aligned and analyzed using software such as SeqMan (DNASTAR, Madison, WI) to determine genotypes at target loci for each participant. This analysis enabled the correlation of genetic polymorphisms with drug efficacy and safety outcomes.

2.3.4. Safety evaluation metrics. The primary safety end points included adverse events reported by participants or identified during clinical assessments, clinically significant deviations observed in laboratory test results, the frequency of hypoglycemic episodes, and overall drug tolerability. Adverse reactions, including nausea, vomiting, diarrhea, rashes, and skin irritation, were systematically documented throughout the treatment period. Participants experiencing intolerable side effects or presenting with clinically significant abnormalities in liver or kidney function tests were withdrawn from the study.

Hypoglycemia was classified according to the 2022 consensus report from the American Diabetes Association and the European Association for the Study of Diabetes.[22] Severe hypoglycemia was defined by the presence of central nervous system symptoms that required external assistance. Mild hypoglycemia was characterized by symptoms associated with a fingerstick glucose level of <3.9 mmol/L, which could be corrected through self-administered dietary intake. Cases presenting with hypoglycemic symptoms but glucose levels exceeding 3.9 mmol/L were classified as symptomatic hypoglycemia without biochemical confirmation.

2.4. Statistical analysis

For the primary efficacy end point, noninferiority tests were employed, while all other statistical analyses were conducted using 2-sided tests. Data analysis was performed using SPSS, version 23.0. Quantitative data conforming to a normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$). Group comparisons or within-group temporal comparisons were executed using either *t* tests or analysis of variance, depending on the data structure. Categorical data were presented as proportions (%) and analyzed using χ^2 tests. A *P* value of <.05 was considered indicative of statistical significance.

The sample size was determined based on the primary efficacy end point, the change in HbA1c 12 weeks from baseline. Setting the noninferiority margin at $\delta = -0.65\%$, with a presumed standard deviation (σ) of 1.4, and targeting power of 85% ($1-\beta = 0.85$) with a type I error rate (α) of 0.05 (one-sided) and a type II error rate (β) of 0.15, calculations were performed using the PASS software designed explicitly for noninferiority trials. This resulted in an initial sample size requirement of 51 participants per group. The sample size was adjusted to 60 participants per group because of potential dropout and exclusion.

3. Results

3.1. Baseline characteristics and participant enrollment

This study initially screened 156 individuals, of whom 129 were randomized. Within the randomized cohort, 66 participants were allocated to the intervention group, and 61 were included

in the final analysis. For the control group, 63 were allocated, and 53 were included in the final analysis (Fig. 1). There were no statistically significant differences between the groups in terms of gender, age, height, weight, BMI, FPG, or HbA1c at baseline, indicating homogeneity across the cohorts ($P > .05$; Table 1).

3.2. HbA1c reduction and achievement rate

After 12 weeks of treatment, the mean reduction in HbA1c levels in the study and control groups were 4.03 ± 1.47% and 4.13 ± 1.50%, respectively. Both groups significantly decreased from baseline ($P < .05$; Table 4). The least squares mean difference in HbA1c reduction between the study and control groups was −0.097, with a 2-sided 95% confidence interval (CI) of −0.646 to 0.446. The lower limit of this CI exceeds the predefined noninferiority margin of −0.65%, indicating that the hypothesis of noninferiority is confirmed under the conditions of this study. At the 12-week mark, the rates of achieving HbA1c targets were assessed. The proportion of patients achieving HbA1c levels of <6.5% was 55.74% (34/61) in the study group and 58.49% (31/53) in the control group. For HbA1c levels below 7.0%, the achievement rates were 80.33% (49/61) in the study group and 71.70% (38/53) in the control group. The P values for these comparisons were .467 and .074, respectively (Fig. 2A), indicating no statistically significant differences between the 2 groups.

3.3. FPG reduction and achievement rates

At 4 weeks, the proportion of patients achieving FPG < 6.1 mmol/L was significantly higher in the study group (26.2% [16/61]) compared with the control group (5.7% [3/53]; $P = .012$; Fig. 2B). The proportion of patients achieving FPG < 7.2 mmol/L was higher in the study group (78.69% [48/61]) than in the control group (66.04% [35/53]), but this difference was not statistically significant ($P = .193$; Fig. 2B). At 12 weeks, no significant differences were observed between the study and control groups regarding FPG achievement rates. The proportions of patients achieving FPG < 6.1 mmol/L were 32.79% (20/61) in the study group and 33.96% (18/53) in the control group. The proportions of patients achieving FPG < 7.2 mmol/L were 78.69% (48/61) in the study group and 81.13% (43/53) in the control group ($P = .937$ and $P = .522$, respectively; Fig. 2C).

The time required to achieve normal FPG levels was significantly shorter in the study group compared with the control

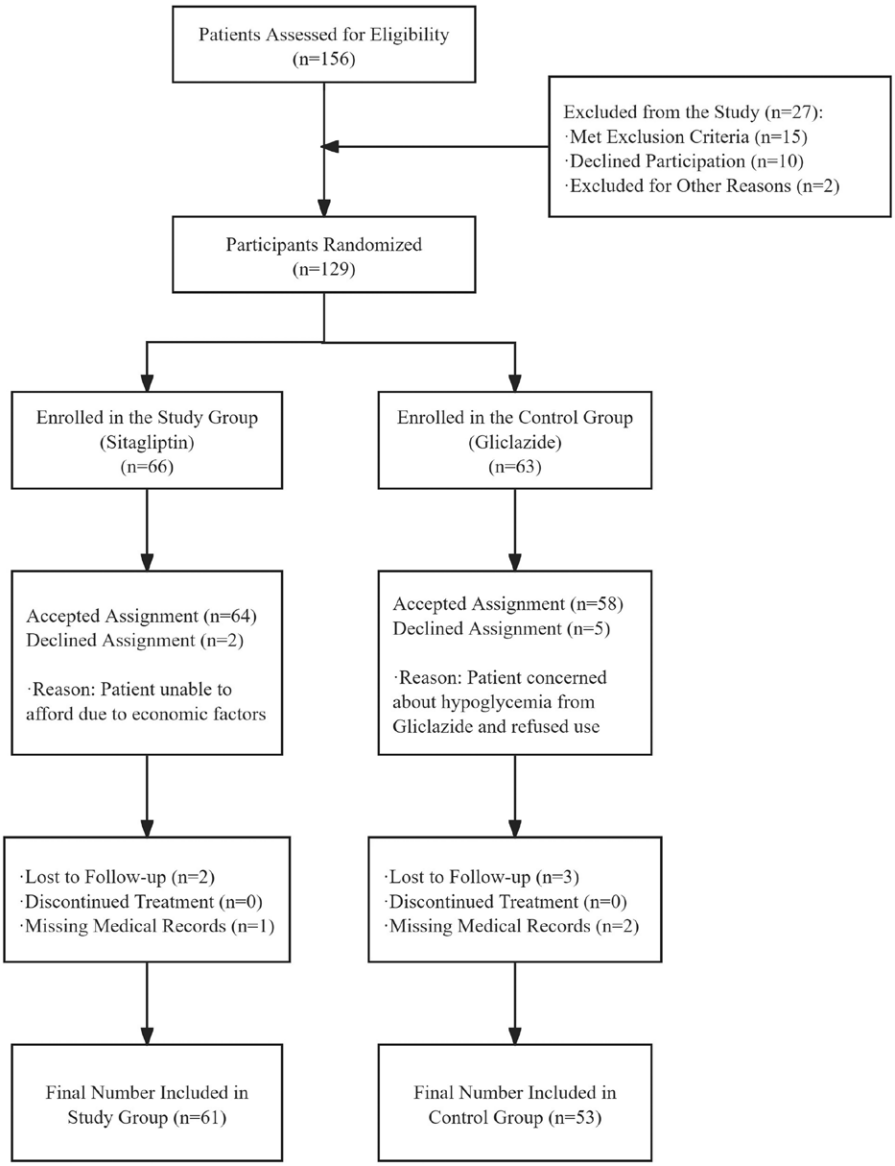

Figure 1. Trial profile.

group (24.56 ± 7.43 vs 28.30 ± 10.29 days; $P = .027$; Table 3; Fig. 2D). Both groups exhibited significant reductions in FPG levels from baseline after 4 weeks of treatment ($P < .05$; Table 2). The study group showed a more significant reduction and lower FPG levels than the control group, with significant differences observed between the groups at 4 weeks ($P < .05$; Table 3; Fig. 3). However, after 12 weeks of treatment, there were no significant differences between the groups regarding FPG levels or reductions from baseline ($P > .05$; Table 4; Fig. 3).

3.4. Changes in body weight and BMI

After 4 weeks of treatment, the study group demonstrated a significant reduction in both weight and BMI from baseline levels. Specifically, weight decreased from 71.73 ± 8.45 to 71.25 ± 8.32 kg, and BMI decreased from 25.00 ± 2.10 to 24.98 ± 2.09 kg/m² ($P < .05$; Table 2). Conversely, the control group showed a significant increase in weight and BMI, with weight increasing from 68.53 ± 9.39 to 68.90 ± 8.88 kg and BMI increasing from 24.51 ± 2.52 to 24.63 ± 2.49 kg/m² ($P < .05$; Table 2). The difference in weight change between the 2 groups was statistically significant (−0.47 ± 0.87 vs 0.38 ± 1.12 kg; $P < .001$; Table 3). At the 12-week mark, although there were no statistically significant changes in weight and BMI from baseline within either group (Table 4), the differences in the magnitude of changes between the 2 groups were significant. The study group experienced a weight change of −0.53 ± 1.85 kg, while the control group had a weight change of 0.49 ± 1.57 kg ($P < .001$). The BMI change was −0.18 ± 0.63 kg/m² in the study group compared with 0.18 ± 0.59 kg/m² in the control group ($P < .001$;

Table 1

Baseline data characteristics of patients in the 2 groups (x̄±s).

Characteristic	Study group (n = 61)	Control group (n = 53)	Difference (95% CI)	t/χ^2	*P* value
Gender (male/female)	47/14	33/20		2.979	.085
Age, yr	48.97 ± 11.34	47.76 ± 9.72	1.21 (−2.75 to 5.17)	0.609	.544
Height, cm	169.25 ± 7.35	167.11 ± 7.24	2.14 (−0.64 to 4.92)	1.553	.123
Weight, kg	71.73 ± 8.45	68.53 ± 9.36	3.20 (−0.14 to 6.54)	1.900	.060
BMI, kg/m²	25.00 ± 2.19	24.51 ± 2.65	0.49 (−0.41 to 1.39)	1.081	.281
FPG, mmol/L	12.66 ± 1.69	12.82 ± 1.78	−0.16 (−0.81 to 0.49)	0.513	.609
HbA1c, %	10.36 ± 1.18	10.64 ± 1.27	−0.28 (−0.72 to 0.16)	1.237	.220
HDL-C, mmol/L	1.05 ± 0.19	1.10 ± 0.21	−0.05 (−0.13 to 0.03)	1.122	.263
LDL-C, mmol/L	3.01 ± 0.73	2.82 ± 0.75	0.19 (−0.09 to 0.47)	1.297	.197
Choc, mmol/L	4.82 ± 0.96	4.75 ± 0.96	0.07 (−0.24 to 0.38)	0.427	.671
TG, mmol/L	1.91 ± 0.94	2.30 ± 1.58	−0.39 (−0.89 to 0.11)	1.594	.114
ALT, U/L	29.04 ± 18.23	32.09 ± 21.90	−3.05 (−10.69 to 4.59)	0.799	.427
AST, U/L	25.63 ± 14.56	25.15 ± 13.42	0.48 (−4.52 to 5.48)	0.178	.859
BUN, mmol/L	5.05 ± 1.10	5.20 ± 1.21	−0.15 (−0.59 to 0.29)	0.682	.497
Cr, μmol/L	56.25 ± 12.37	54.22 ± 8.58	2.03 (−2.05 to 6.11)	0.987	.327

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, BUN = blood urea nitrogen, CI = confidence interval, Cr = creatinine, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglycerides.

Table 2

Values of each index before and after 4 and 12 weeks of treatment and changes compared with baseline (x̄±s).

Index	Group	Baseline (x̄±s)	4 wk (x̄±s)	*P* value (4 wk)	12 wk (x̄±s)	*P* value (12 wk)
FPG, mmol/L	Sitagliptin	12.66 ± 1.69	6.61 ± 0.84	<.001*	6.47 ± 0.79	<.001*
	Gliclazide	12.82 ± 1.78	6.94 ± 0.71	<.001*	6.44 ± 0.72	<.001*
Weight, kg	Sitagliptin	71.73 ± 8.45	71.25 ± 8.32	<.001*	71.04 ± 8.87	.052
	Gliclazide	68.53 ± 9.39	68.90 ± 8.88	.019*	67.67 ± 9.84	.066
BMI, kg/m²	Sitagliptin	25.00 ± 2.10	24.98 ± 2.09	<.001*	24.67 ± 2.36	.055
	Gliclazide	24.51 ± 2.52	24.63 ± 2.49	.013*	24.41 ± 2.89	.071
HbA1c, %	Sitagliptin	10.36 ± 1.18			6.43 ± 0.54	<.001*
	Gliclazide	10.64 ± 1.27			6.51 ± 0.65	<.001*

BMI = body mass index, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin.
*$P < .05$, indicating statistical significance.

Table 3

Comparison of all indexes after 4 weeks of treatment (x̄±s).

Index	Study group (x̄±s)	Control group (x̄±s)	Difference (95% CI)	*t*	*P* value
Time to achieve target glucose, d	24.56 ± 7.43	28.30 ± 10.29	−3.74 (−6.86 to −0.62)	−2.247	.027*
FPG, mmol/L	6.61 ± 0.84	6.94 ± 0.71	−0.33 (−0.61 to −0.05)	−2.297	.022*
ΔFPG, mmol/L	−6.05 ± 1.98	−5.88 ± 1.93	−0.17 (−0.87 to 0.53)	0.461	.646
Weight, kg	71.25 ± 8.32	68.90 ± 8.88	2.35 (−0.83 to 5.53)	1.462	.147
ΔWeight, kg	−0.47 ± 0.87	0.38 ± 1.12	−0.85 (−1.22 to −0.48)	−4.507	<.001*
BMI, kg/m²	24.84 ± 2.17	24.63 ± 2.49	0.21 (−0.77 to 1.19)	0.464	.643
ΔBMI, kg/m²	−0.16 ± 0.31	−0.12 ± 0.16	−0.28 (−0.54 to −0.02)	−1.792	.076

BMI = body mass index, CI = confidence interval, FPG = fasting plasma glucose, Δ = change from baseline.
*$P < .05$, indicating statistical significance.

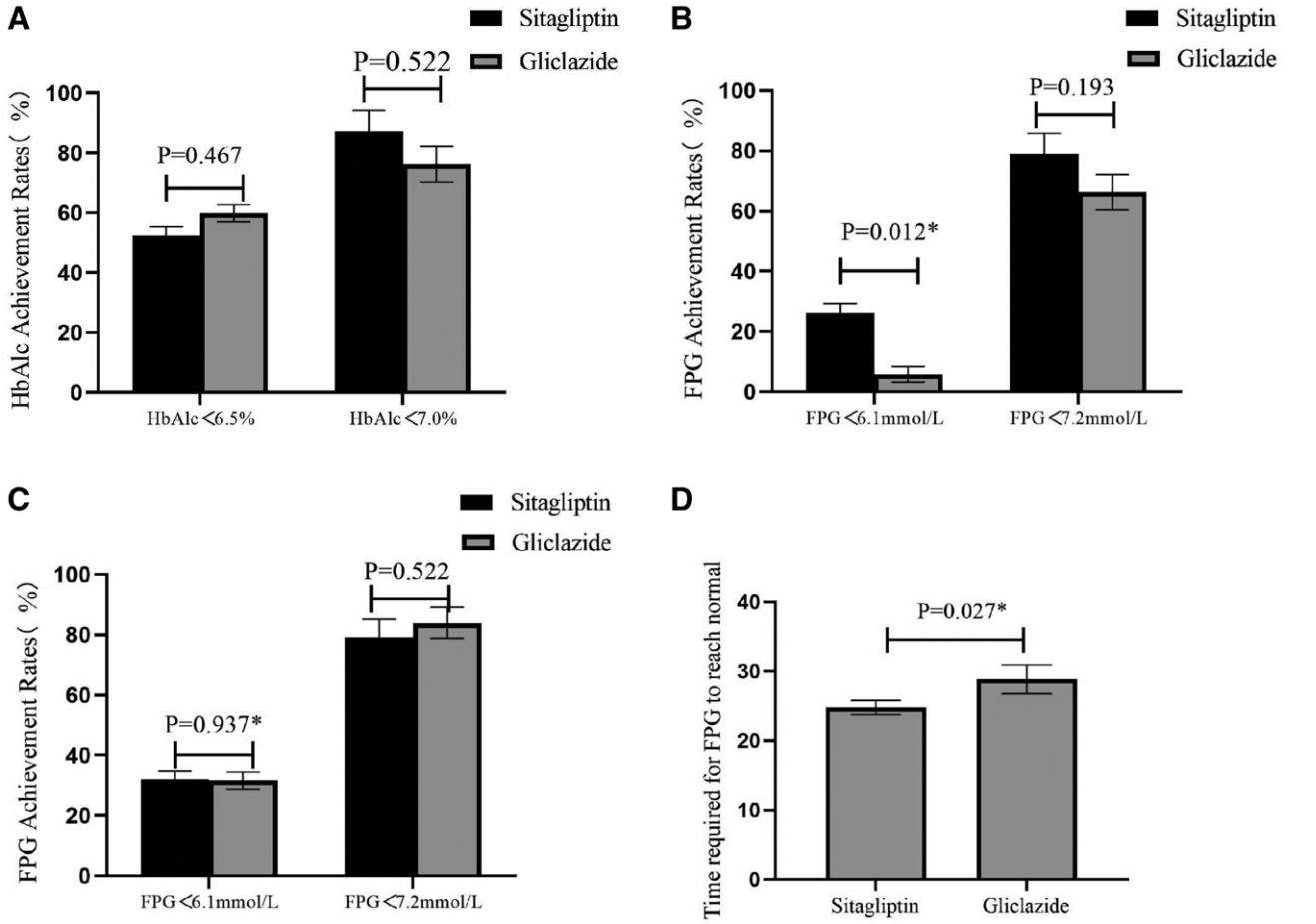

Figure 2. Comparison of changes in fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) levels between the sitagliptin and gliclazide groups. The sitagliptin group had a shorter time to achieve target FPG levels, lower FPG levels, and a higher proportion of patients achieving FPG < 6.1 mmol/L after 4 weeks, suggesting that sitagliptin can control hyperglycemia more effectively and in a shorter time. (A) Comparison of HbA1c achievement rates between the 2 groups after 12 weeks of treatment. (B) Comparison of FPG achievement rates between the 2 groups after 4 weeks of treatment. (C) Comparison of FPG achievement rates between the 2 groups after 12 weeks of treatment.

Table 4). Thus, sitagliptin treatment reduces weight and BMI, whereas gliclazide treatment may increase these parameters.

3.5. Evaluation of islet β-cell function

At the 12-week mark, an oral glucose tolerance test was conducted to evaluate the insulin resistance and islet β-cell function. The assessment included the indices HOMA-IR, HOMA-β, AUC-PG, AUC-INS, $\Delta I_{60}/\Delta G_{60}$, I_p/I_0, DI, and MBCI. No significant differences were observed between the 2 groups across these indices ($P > .05$; Table 5). Specifically, the HOMA-IR values were 3.29 ± 1.27 versus 4.74 ± 2.78 ($P = .073$). The HOMA-β values were 121.77 ± 91.68 versus 95.07 ± 81.84 ($P = .266$). The AUC-PG values were 29.28 ± 15.21 versus 30.83 ± 8.32 ($P = .707$; Fig. 4A). The AUC-INS values were 125.85 ± 84.37 versus 145.32 ± 63.29 ($P = .466$; Fig. 4B). The $\Delta I_{60}/\Delta G_{60}$ values were 10.39 ± 5.17 versus 13.76 ± 8.67 ($P = .087$). The I_p/I_0 values were 5.09 ± 3.21 versus 5.04 ± 3.50 ($P = .967$). The DI values were 3.64 ± 4.54 versus 3.68 ± 5.28 ($P = .973$). Finally, the MBCI values were 7.80 ± 5.56 versus 10.05 ± 10.25 ($P = .447$). These findings suggest no statistically significant differences in islet β-cell function between the study and control groups after 12 weeks of treatment.

3.6. Genetic polymorphisms and therapeutic efficacy

The analysis revealed significant effects of DPP-4 gene polymorphisms on the efficacy of sitagliptin. Patients with the rs2909451 TT genotype in the study group (treated with sitagliptin) exhibited a median HbA1c improvement of 0.57 (interquartile range [IQR], 0.18–0.85), whereas the control group (treated with gliclazide) showed a median improvement of 1.11 (IQR, 0.86–1.35; $P < .001$). Similarly, for the rs4664443 GG genotype, the median HbA1c improvement in the study group was 0.69 (IQR, 0.48–0.91) compared with 1.25 (IQR, 1.00–1.46) in the control group ($P < .001$), indicating lower efficacy of sitagliptin.

Regarding GLP1R gene polymorphisms, patients with the rs6923761 AA homozygous genotype in the study group had a median HbA1c improvement of 0.90 (IQR, 0.61–1.01), while the control group showed 1.41 (IQR, 1.12–1.45; $P = .010$), suggesting reduced glycemic response to sitagliptin. Conversely, patients with the rs3765467 AG genotype in the study group demonstrated a median HbA1c improvement of 1.42 (IQR, 1.22–1.68) compared with 1.08 (IQR, 0.97–1.15) in the control group ($P = .023$), indicating favorable responses to both treatments.

KCNQ1 gene polymorphisms also significantly affected treatment outcomes. Patients with the rs163184 GG allele in the study group had a median HbA1c improvement of 0.81 (IQR, 0.62–0.92) compared with 1.16 (IQR, 0.91–1.32) in the control group ($P < .001$), suggesting lower responsiveness to sitagliptin and better response to gliclazide. For KCNJ11 gene polymorphisms, patients with the rs2285676 CC genotype in the study group had a median HbA1c improvement of 1.02 (IQR, 0.90–1.22), while the control group showed 1.31 (IQR, 1.08–1.42;

$P < .001$), indicating more substantial insulin secretion capability with sitagliptin.

CDKAL1 gene variants, specifically rs7754840 CG and rs756992 AG, were associated with more significant HbA1c reductions in the study group. Patients with the rs7754840 CG genotype showed a median improvement of 1.44 (IQR, 1.38–1.72) in the study group compared with 1.09 (IQR, 0.79–1.17) in the control group ($P = .053$). Similarly, patients with the rs756992 AG genotype exhibited a median improvement of 1.43 (IQR, 1.28–1.52) in the study group compared with 1.10 (IQR, 0.87–1.18) in the control group ($P = .081$). CYP2C9 gene polymorphisms also significantly influenced treatment efficacy. Patients with the rs1799853 TT genotype in the study group had a median HbA1c improvement of 0.70 (IQR, 0.69–0.72), while the control group showed 1.07 (IQR, 0.82–1.42; $P < .001$).

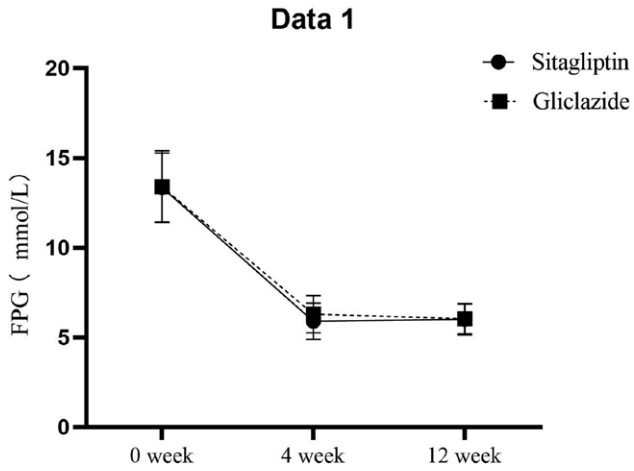

Figure 3. The change trend of fasting plasma glucose (FPG).

For the rs1057910 GG genotype, the study group exhibited a median improvement of 0.93 (IQR, 0.66–1.21) compared with 1.20 (IQR, 0.89–1.30) in the control group ($P = .464$). These findings suggest that rs1799853 and rs1057910 variants lead to slower metabolism of gliclazide, thereby impacting drug efficacy and adverse event rates (Table 6; Fig. 5).

The Manhattan plot shows the overall distribution of single-nucleotide polymorphism associations across the genome, highlighting key loci such as rs2909451, rs4664443, rs163184, and rs2285676, which are strongly associated with differential HbA1c improvements and underscore the genetic influence on therapeutic response (Fig. 6).

3.7. Adverse event monitoring and safety assessment

Adverse events were systematically collected and recorded throughout the 12-week treatment period. At each follow-up visit, patients were proactively asked about any symptoms or discomfort they experienced. In addition, patients were provided with symptom diaries to record any adverse events between visits. Adverse events were classified into those related to the study drugs (e.g., hypoglycemia, nausea, vomiting, and diarrhea) and those unrelated (e.g., common cold).

During the 12-week treatment period, hypoglycemic symptoms were observed in 4 patients (6.6%, 4/61) in the study group versus 5 patients (9.4%, 5/53) in the control group (95% CI, −0.128 to 0.072; $P = .605$). Two cases of mild hypoglycemia were reported in the control group, which resolved after self-administered food intake. In addition, nausea was reported in 3 patients (4.9%, 3/61) in the study group versus 4 patients (7.5%, 4/53) in the control group (95% CI, −0.105 to 0.053; $P = .692$). Vomiting occurred in 2 patients (3.3%, 2/61) in the study group versus 3 patients (5.7%, 3/53) in the control group (95% CI, −0.094 to 0.048; $P = .653$). Diarrhea was reported in 5 patients (8.2%, 5/61) in the study group versus 6 patients (11.3%, 6/53) in the control group (95% CI, −0.137 to 0.073;

Table 4

Comparison of all indexes after 12 weeks of treatment (x̄±s).

Index	Study group (x̄±s)	Control group (x̄±s)	Difference (95% CI)	*t*	*P* value
FPG, mmol/L	6.47 ± 0.79	6.44 ± 0.72	0.03 (−0.246 to 0.306)	0.169	.866
ΔFPG, mmol/L	−6.19 ± 1.93	−6.38 ± 2.08	0.19 (−0.549 to 0.929)	−0.509	.612
Weight, kg	71.04 ± 8.87	67.67 ± 9.84	3.37 (−0.087 to 6.827)	1.671	.098
ΔWeight, kg	−0.53 ± 1.85	0.49 ± 1.57	−1.02 (−1.647 to −0.393)	−2.686	.009*
BMI, kg/m²	24.67 ± 2.36	24.41 ± 2.89	0.26 (−0.718 to 1.238)	0.464	.646
ΔBMI, kg/m²	−0.18 ± 0.63	0.18 ± 0.59	−0.36 (−0.583 to −0.137)	−2.678	.009*
HbA1c, %	6.43 ± 0.54	6.51 ± 0.65	−0.08 (−0.302 to 0.142)	−0.716	.476
ΔHbA1c, %	−4.03 ± 1.47	−4.13 ± 1.50	−0.097 (−0.646 to 0.446)	−0.351	.726

BMI = body mass index, CI = confidence interval, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, Δ = change from baseline.
*$P < .05$, indicating statistical significance.

Table 5

Comparison of islet cell function between the 2 groups (x̄±s).

Index	Study group (x̄±s)	Control group (x̄±s)	Difference (95% CI)	*t*	*P* value
HOMA-IR	3.29 ± 1.27	4.74 ± 2.78	−1.45 (−2.263 to −0.637)	−1.830	.073
HOMA-β	121.77 ± 91.68	95.07 ± 81.84	26.70 (−5.15 to 58.55)	1.126	.266
AUC-PG	29.28 ± 15.21	30.83 ± 8.32	−1.55 (−5.98 to 2.88)	−0.378	.707
AUC-INS	125.85 ± 84.37	145.32 ± 63.29	−19.47 (−46.65 to 7.71)	−0.736	.466
$\Delta I_{60}/\Delta G_{60}$	10.39 ± 5.17	13.76 ± 8.67	−3.37 (−7.17 to 0.43)	−1.746	.087
I_p/I_0	5.09 ± 3.21	5.04 ± 3.50	0.05 (−1.13 to 1.23)	0.042	.967
DI	3.64 ± 4.54	3.68 ± 5.28	−0.04 (−1.93 to 1.85)	−0.035	.973
MBCI	7.80 ± 5.56	10.05 ± 10.25	−2.25 (−5.88 to 1.38)	−0.767	.447

AUC-INS = area under the curve for insulin, AUC-PG = area under the curve for plasma glucose, CI = confidence interval, DI = disposition index, HOMA-IR = homeostatic model assessment of insulin resistance, HOMA-β = homeostatic model assessment of β-cell function, I_p/I_0 = peak insulin-to-baseline insulin ratio, MBCI = modified β-cell function index, $\Delta I_{60}/\Delta G_{60}$ = incremental insulin-to-glucose ratio at 60 minutes.

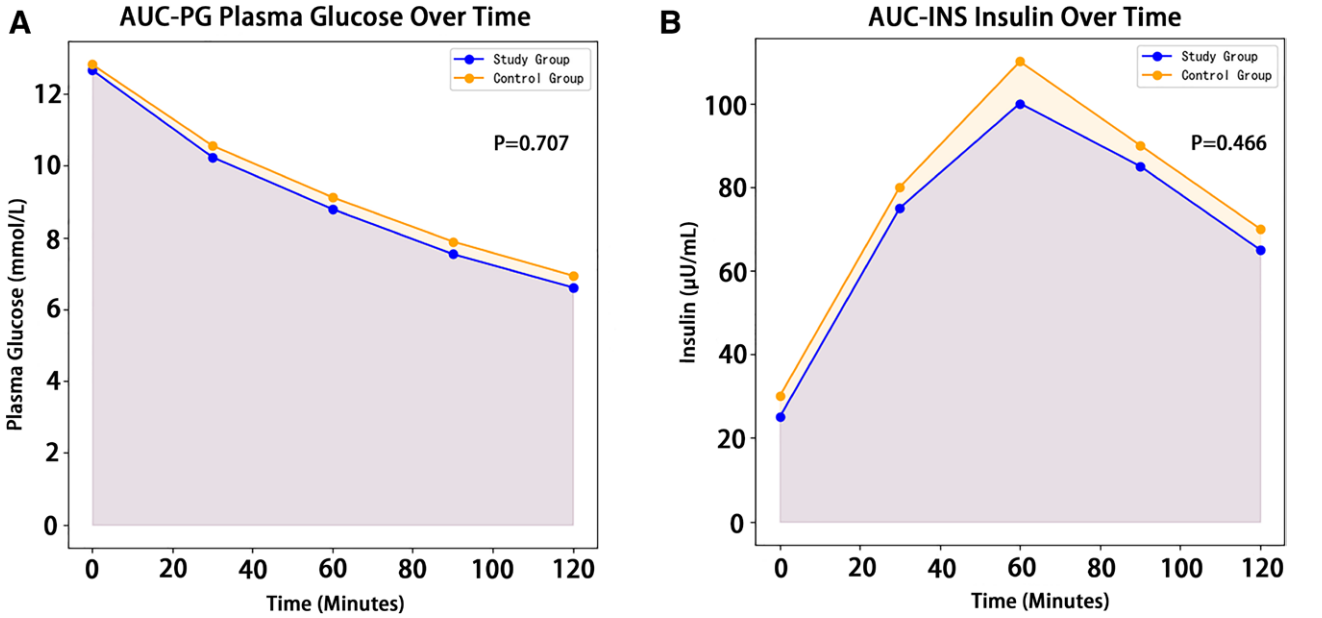

Figure 4. Comparison of plasma glucose and insulin levels over time between study and control groups. (A) Plasma glucose (mmol/L): both the study group (blue line) and control group (orange line) showed a gradual decline in plasma glucose levels over 120 minutes, with the study group demonstrating a slightly greater reduction, indicating potentially more effective glycemic control. (B) Insulin (μU/mL): insulin levels in both groups increased rapidly within the first 60 minutes, followed by a gradual decline. The study group exhibited a slightly lower peak insulin level, suggesting better insulin sensitivity. AUC-INS = area under the curve for insulin, AUC-PG = area under the curve for plasma glucose.

P = .753). No other adverse reactions were reported (Table 7; Fig. 7).

4. Discussion

In clinical practice, the treatment choices for newly diagnosed patients with T2DM, particularly those with significant glucotoxicity, are often influenced by factors such as pharmacoeconomics, adherence, and the risk of adverse events. This study provides a detailed comparison between sitagliptin and gliclazide, offering valuable evidence for clinicians to optimize treatment strategies in real-world settings. In the diabetic population, treatment-naive patients with T2DM constitute a unique and complex subgroup. Optimizing glycemic control strategies remains a significant challenge for endocrinologists. Although international guidelines, such as those from the American Diabetes Association, provide recommendations, the choice of therapeutic regimens in clinical practice within China and other developing countries is influenced by various factors, including drug availability, pharmacoeconomics, and national medical policies. Consequently, there is ongoing debate regarding the optimal treatment approach. This study specifically targeted this patient subgroup. The findings indicate that compared with gliclazide, sitagliptin combined with metformin resulted in more rapid reductions in blood glucose levels and a higher compliance rate for FPG. In addition, there was a trend towards reductions in body weight and BMI with sitagliptin, whereas gliclazide was associated with increased parameters. Although the incidence of hypoglycemic events was higher in the gliclazide group compared with the sitagliptin group, this difference was not statistically significant. In summary, sitagliptin combined with metformin provides a more effective and safer treatment option, with greater convenience and better patient compliance, compared with gliclazide, for treatment-naive patients with T2DM.

Glucotoxicity of pancreatic β cells is a significant cause of β-cell dysfunction. Prolonged exposure to high glucose levels induces the inactivation of β-cell-specific transcription factors, triggers β-cell apoptosis, inhibits β-cell secretory functions, and ultimately leads to β-cell failure.[23] If not addressed promptly, this can result in irreversible pancreatic cell damage.[24] Thus, early intervention to alleviate glucotoxicity is crucial for maximizing the recovery and protection of pancreatic β-cell function.[25]

Further research has identified various factors contributing to glucotoxicity-induced β-cell dysfunction, including altered glycolysis, mitochondrial dysfunction, oxidative stress, and impaired insulin secretion.[26–28] Strategies aimed at inhibiting mTOR, optimizing phenolic extraction, and utilizing pharmacological interventions to preserve β cells are under investigation to mitigate the effects of glucotoxicity.[29–31] Moreover, the persistence of glucotoxicity-induced β-cell failure is closely associated with the progression of T2DM.[32] Mechanistic studies reveal that impaired insulin secretion, increased reactive oxygen species production, and mitochondrial dysfunction contribute to sustained hyperglycemia.[33,34] Addressing glucotoxicity requires a comprehensive understanding of its impact on cellular processes, such as L-cell differentiation impairment and β-cell dedifferentiation.[35]

Table 6

Comparison of the median (IQR) glycated hemoglobin improvement and *P* values between the study group and control group across different genotypes.

Genotype	Study group, median (IQR)	Control group, median (IQR)	*P* value
rs2909451 TT	0.57 (0.18–0.85)	1.11 (0.86–1.35)	<.001
rs4664443 GG	0.69 (0.48–0.91)	1.25 (1.00–1.46)	<.001
rs6923761 AA	0.90 (0.61–1.01)	1.41 (1.12–1.45)	.010
rs3765467 AG	1.42 (1.22–1.68)	1.08 (0.97–1.15)	.023
rs163184 GG	0.81 (0.62–0.92)	1.16 (0.91–1.32)	<.001
rs2285676 CC	1.02 (0.90–1.22)	1.31 (1.08–1.42)	<.001
rs7754840 CG	1.44 (1.38–1.72)	1.09 (0.79–1.17)	.053
rs756992 AG	1.43 (1.28–1.52)	1.10 (0.87–1.18)	.081
rs1799853 TT	0.70 (0.69–0.72)	1.07 (0.82–1.42)	<.001
rs1057910 GG	0.93 (0.66–1.21)	1.20 (0.89–1.30)	.464

IQR = interquartile range.

Studies have demonstrated that short-term intensive insulin therapy is highly effective in reducing glucotoxicity. This approach rapidly alleviates hyperglycemia, improves insulin resistance, and restores pancreatic β-cell function.[36] However, the clinical application of insulin therapy is often fraught with challenges: some patients are reluctant to initiate insulin therapy due to fear of injections or hypoglycemia, and there can be significant issues such as blood glucose fluctuations, weight gain, and injection errors.[37] For the long-term management of chronic diseases, oral medications offer distinct advantages.[38] Consequently, it is imperative to explore and optimize treatment regimens to meet the individualized needs of patients.

GLP-1 is an incretin hormone that promotes insulin secretion in a glucose-dependent manner. In addition, it inhibits glucagon secretion, maintains glucose homeostasis, and delays gastric emptying.[39] Incretin-based drugs, specifically DPP-4 inhibitors,

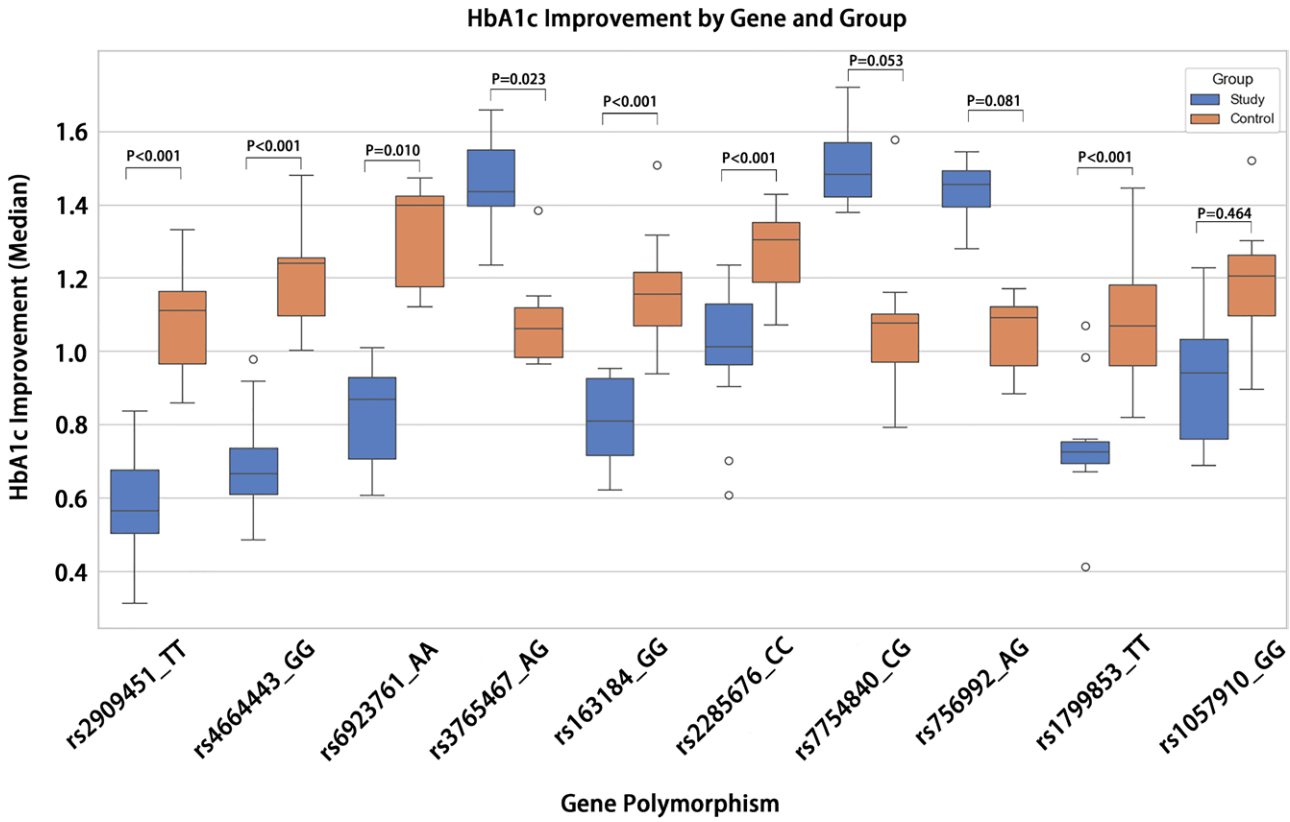

Figure 5. Glycated hemoglobin (HbA1c) improvement by gene polymorphism and treatment group. Note: median HbA1c improvement (with interquartile ranges) for patients with different gene polymorphisms in the study group (treated with sitagliptin) versus the control group (treated with gliclazide). Each box plot represents the distribution of HbA1c improvement for a specific genotype, highlighting the variability in treatment response associated with genetic differences. The study group is depicted in blue, while the control group is depicted in orange. Significant differences in median HbA1c improvement are observed between the 2 groups for several polymorphisms, indicating the influence of genetic variability on treatment efficacy.

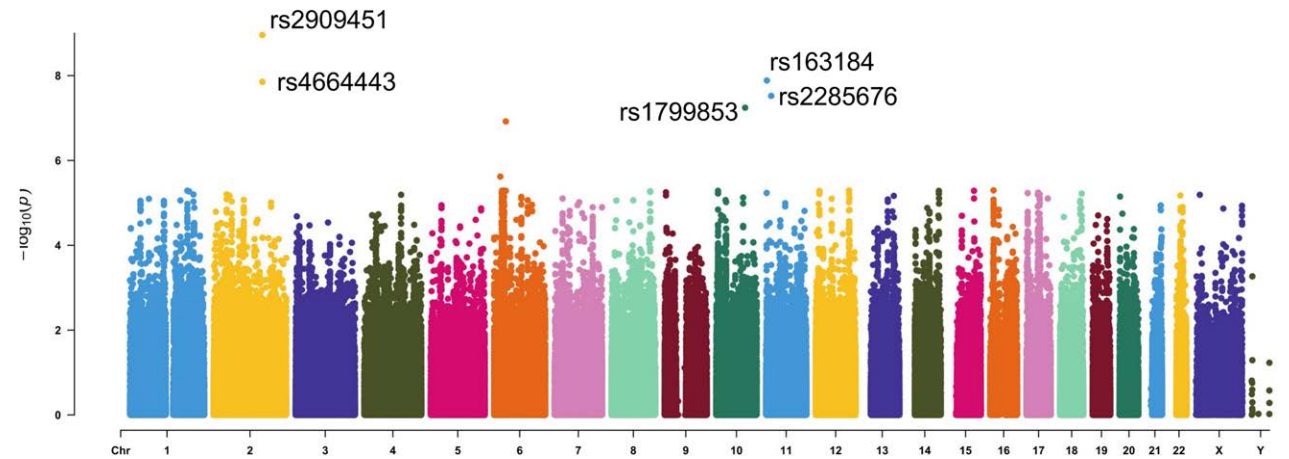

Figure 6. Manhattan plot of genome-wide association analysis for glycated hemoglobin (HbA1c) improvement in patients with type 2 diabetes mellitus (T2DM). Manhattan plot displaying the genome-wide association results for HbA1c improvement in treatment-naive patients with T2DM. The *x* axis represents chromosomal positions, and the *y* axis represents the $-\log_{10}(p)$ values. Key loci, including rs2909451, rs4664443, rs163184, rs2285676, and rs1799853, are highlighted due to their significant associations with therapeutic response.

Table 7

Adverse events during the 12-week treatment period.

Adverse event	Study group (n = 61)	Control group (n = 53)	Difference (95% CI)	*t*	*P* value
Hypoglycemia	4 (6.6%)	5 (9.4%)	−2.8% (−0.128 to 0.072)	−0.528	.605
Nausea	3 (4.9%)	4 (7.5%)	−2.6% (−0.105 to 0.053)	−0.398	.692
Vomiting	2 (3.3%)	3 (5.7%)	−2.4% (−0.094 to 0.048)	−0.456	.653
Diarrhea	5 (8.2%)	6 (11.3%)	−3.1% (−0.137 to 0.073)	−0.325	.753

CI =confidence interval.

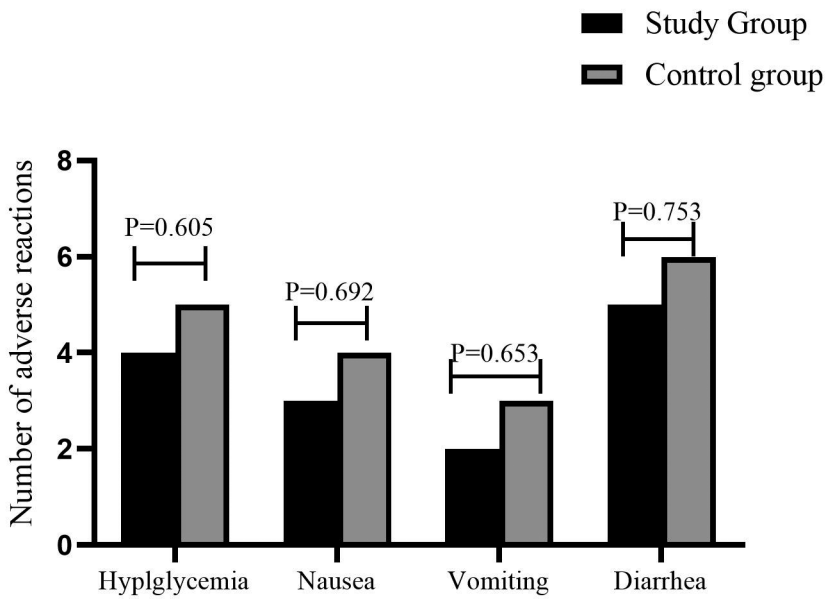

Figure 7. Adverse events during the 12-week treatment period.

degrade and inactivate the DPP-4 enzyme, leading to a 2- to 3-fold increase in endogenous GLP-1 levels.[5,40] Sitagliptin is a highly selective DPP-4 inhibitor that enhances glucose control by increasing endogenous GLP-1 levels, thereby increasing insulin release and reducing glucagon levels in the bloodstream.[41] Sitagliptin, whether used as monotherapy or combined with other oral antidiabetic drugs, is well-tolerated. It offers the advantages of a convenient once-daily oral regimen, a neutral effect on body weight, a low risk of hypoglycemia, and a favorable efficacy and safety profile, making it a valuable option for treating patients with T2DM.[42,43]

Hypoglycemia is a common complication of diabetes and may serve as a significant risk factor for morbidity and mortality among patients with diabetes.[7] Traditional antidiabetic agents, such as sulfonylureas, are associated with a risk of hypoglycemia.[6] In contrast to traditional secretagogues, DPP-4 inhibitors promote insulin secretion in a glucose-dependent manner, lowering the risk of hypoglycemia while reducing blood glucose levels. A recent meta-analysis encompassing 58 randomized controlled trials demonstrated that DPP-4 inhibitors significantly reduce FPG and HbA1c levels, with a low incidence of hypoglycemia.[44] Our study revealed no statistically significant difference in the incidence of hypoglycemia between the 2 groups. This outcome can be attributed to 2 primary factors. First, the study population consisted of treatment-naive patients with diabetes with relatively preserved pancreatic function and normal liver and kidney function, which may have contributed to an adequate compensatory response to hypoglycemia. Second, the duration of antidiabetic drug administration in this study was limited to 1 month, which is relatively short; hence, the incidence of hypoglycemia requires further observation over an extended period.

It is well-established that ≈80% of patients with diabetes are overweight or obese, and weight gain exacerbates insulin resistance and increases the risk of diabetic complications.[45] This study found sitagliptin to improve glycemic control and positively influence body weight. After 1 month of treatment, the sitagliptin group demonstrated a reduction in body weight and BMI compared with baseline levels, whereas the gliclazide group exhibited an increase in these parameters. At 3 months, the difference in the extent of weight change between the 2 groups was statistically significant, suggesting that gliclazide is associated with weight gain, whereas sitagliptin is not. This observation is consistent with findings from previous studies.[46] Therefore, for treatment-naive patients with glucotoxicity, sitagliptin is more favorable than gliclazide in managing body weight and BMI.

Animal studies have demonstrated that DPP-4 inhibitors can prevent cellular damage and apoptosis in murine models, preserve islet architecture, improve the HOMA-β index, promote β-cell regeneration, and concurrently suppress α-cell proliferation.[47] Compared with glipizide, sitagliptin has been shown to restore the α/β-cell ratio and normalize islet morphology.[48] Clinical studies have also indicated that 3 months of sitagliptin treatment significantly improve islet function markers, such

as the HOMA-β index and the proinsulin/insulin ratio.[49,50] Furthermore, sitagliptin enhances insulin signaling and insulin sensitivity in human adipose tissue.[51]

In the present study, no significant differences were observed between the 2 drugs in terms of improving β-cell function-related markers. This lack of difference can be attributed to 2 primary factors. First, the current β-cell function evaluation indices are predominantly based on fasting insulin and fasting glucose levels. Given that our study population comprised treatment-naive patients with diabetes with relatively preserved β-cell function, no significant differences in fasting insulin and glucose levels were detected. Second, the duration of antidiabetic drug administration in this study was limited to 1 month, which is relatively short; therefore, more extended observation periods are necessary to assess β-cell function markers further.

The efficacy of sitagliptin, a DPP-4 inhibitor, can be influenced by genetic variations in the DPP-4 gene. Specifically, individuals with specific genotypes, such as the TT genotype of rs2909451 and GG genotype of rs4664443, may experience lower efficacy of sitagliptin.[52] Moreover, a genome-wide association study identified a polymorphism in PRKD1 (rs57803087) that was associated with a more significant response to DPP-4 inhibitors such as sitagliptin in individuals with type 2 diabetes.[53] As a DPP-4 inhibitor, sitagliptin has been shown to regulate oxidative stress and autophagy, indicating its effectiveness in mitigating hypoxia-induced injury in various cells, including cardiomyocytes.[54] In addition, DPP-4 inhibitors, including sitagliptin, have demonstrated significant anti-inflammatory actions in both in vivo and in vitro models, further supporting their therapeutic potential.[55] Furthermore, DPP-4 inhibitors such as sitagliptin inhibit the degradation of GLP-1, thereby prolonging its effects, which can be beneficial in managing diabetes.[56] Sitagliptin has also been found to provide significant DPP-4 inhibition, crucial for its efficacy in treating diabetes.[57]

The CYP2C9 enzyme is crucial for the metabolism of gliclazide. Variants such as CYP2C9*2 (rs1799853) and CYP2C9*3 (rs1057910) are associated with reduced enzyme activity and slower metabolic rates, impacting the metabolism of drugs such as gliclazide.[58,59] Similarly, CYP2C19 is involved in gliclazide metabolism. Gene polymorphisms such as CYP2C19*2 (rs4244285) and CYP2C19*3 (rs4986893) result in reduced enzyme activity and slower metabolism, affecting the efficacy and safety of medications metabolized by CYP2C19, including gliclazide.[60]

This study is subject to several limitations, including a small sample size and a short observation period. Larger sample sizes and longer duration randomized controlled trials are warranted to explore further the effects of these 2 drugs on β-cell function and the incidence of adverse reactions.

In conclusion, this study found that for treatment-naive patients with T2DM and glucotoxicity, sitagliptin combined with metformin is noninferior to gliclazide combined with metformin in terms of glycemic control. The sitagliptin group achieved more rapid reductions in blood glucose levels and higher FPG compliance rates and showed a trend towards reductions in body weight and BMI, with a similar risk of hypoglycemia. Genetic polymorphisms, such as DPP-4 rs2909451 TT and rs4664443 GG, significantly influenced the efficacy of sitagliptin, highlighting the importance of personalized medicine. Therefore, considering the overall efficacy and safety profile, sitagliptin combined with metformin represents a convenient and effective alternative to insulin therapy for patients who encounter difficulties with insulin injections.

5. Conclusion

This study demonstrated that compared with traditional sulfonylureas, DPP-4 inhibitors not only effectively improved glycemic control but also significantly reduced the risk of weight gain. Their therapeutic benefits were particularly evident in patients with significant glucotoxicity, suggesting broader applicability and potential advantages in preserving β-cell function. In addition, the genetic polymorphism analysis identified specific DPP-4 gene loci associated with the efficacy of sitagliptin, addressing gaps in prior research regarding genotype-specific responses and underscoring the critical role of genetic background in guiding drug selection. Furthermore, quantitative metrics such as HbA1c reduction rates reinforced the established association between gliclazide and CYP2C9 gene polymorphisms, especially in patients with glucotoxicity, highlighting distinct genotype-dependent therapeutic responses. These findings provide new insights into optimizing treatment strategies and support the integration of genetic information into clinical decision-making to develop personalized therapeutic approaches. Collectively, incorporating genetic background into clinical practice may enhance treatment efficacy, reduce unnecessary adverse events, and advance the goals of precision medicine. Moreover, the results emphasized the importance of achieving rapid glycemic control and highlighted the advantages of DPP-4 inhibitors in early intervention, offering valuable guidance for the clinical management of patients with significant glucotoxicity.

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