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Original Article

Influence of glimepiride plus sitagliptin on treatment outcome, blood glucose, and oxidative stress in diabetic patients

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Abstract: Objective: This research sets out to investigate the influence of glimepiride (GLIM) plus sitagliptin (SITA) on the treatment outcome, blood glucose (BG), and oxidative stress (OS) in diabetic patients. Methods: In this retrospective study, 189 patient cases of type 2 diabetes mellitus (T2DM) admitted from July 2017 to July 2021 to the Affiliated Hospital of Nantong University were selected, of whom 99 cases treated with GLIM + SITA were assigned to the research group (RG) and 90 cases receiving GLIM monotherapy were set as the control group (CG). The two cohorts of patients were compared in terms of treatment outcomes, BG, islet function, OS, inflammatory responses (IRs), and safety. The BG indexes detected mainly included fasting blood glucose (FBG), 2-hour postprandial blood glucose (2hPG) and glycosylated hemoglobin (HbA1c). Islet function was mainly measured by Homeostasis Model Assessment of β-cell Function (HOMA-β) and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). The OS parameters measured primarily included malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX). Tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-18 were the inflammatory factors measured. Results: A statistically higher excellent or good rate of treatment was determined in the RG compared to the CG. After treatment, FBG, 2hPG, HbA1c, HOMA-IR, MDA, TNF-α, IL-6, and IL-18 were lower in the RG while HOMA-β, SOD, and GSH-PX were higher, compared to the levels before treatment and the CG. A non-significantly different incidence of adverse reactions between groups was determined. Conclusions: Our findings demonstrated high efficacy of GLIM + SITA in the treatment of T2DM patients, which can effectively improve the BG and OS of patients and reduce inflammation without increasing the incidence of adverse reactions. This should have high clinical application value.

Keywords: Glimepiride, sitagliptin, diabetes, treatment outcome, blood glucose, oxidative stress, inflammatory response

Introduction

With an increasing incidence, diabetes is a common chronic metabolic disease that affects about one in ten Americans [1, 2]. According to epidemiological data of the disease, the number of diabetic patients in the world has reached 463 million, mainly affecting people aged between 20 and 79 [3, 4]. Diabetes is associated with abnormal blood glucose (BG) metabolism that may be attributed to factors such as insufficient insulin production or insensitivity of cells to insulin [5]. The pathogenesis of diabetes is complex. Oxidative stress (OS) and inflammatory responses (IRs) are known to mediate the progression of diabetes [6]. It is shown that excessive reactive oxygen species (ROS) will be induced in a hyperglycemic environment to activate OS, leading to a series of adverse events such as organ damage, IRs, and insulin resistance in the host [7]. In addition, OS may directly damage insulin-secreting pancreatic β cells, thus inhibiting insulin sensitivity and inducing the occurrence and development of diabetes [8]. Currently, the therapeutic effect of diabetes is still unsatisfactory. Hence, it carries huge implications for the management optimization of such patients to explore more effective and reliable therapeutic strategies from the perspectives of curative efficacy, BG, OS, and IRs.

As a sulfonylurea, glimepiride (GLIM) is commonly used as a hypoglycemic agent for type 2 diabetes mellitus (T2DM) [9]. It mainly regulates insulin resistance and insulin sensitivity by stimulating pancreatic β cells to secrete insulin, thereby exerting anti-T2DM therapeutic effects [10]. Chen et al. [11] reported in their study that GLIM can be combined with recombinant human insulin injection to relieve OS and abnormal BG in T2DM, and prevent osteoporosis and other complications, suggesting that GLIM has effectiveness and safety in T2DM. Sitagliptin (SITA) is a potent dipeptidyl peptidase inhibitor that can be used alone or in combination with other hypoglycemic agents to play a therapeutic role [12]. It has been reported that SITA not only has efficacy in the treatment of diabetes, but is cost-effective compared to pioglitazone and metformin [13]. Ishii et al. [14] indicated in their study that SITA plus GLIM was well tolerated and effective in T2DM patients, which can significantly reduce glycosylated hemoglobin (HbA1c) without affecting patients' weight or causing hypoglycemia.

Because there are few related studies on the multi-dimensional effects of GLIM plus SITA on the treatment outcome, BG, OS and IR of T2DM patients, we conducted this research to provide new insight into T2DM treatment.

Data and methods

General case data

In this retrospective study, 189 diabetic patients, who all had T2DM, admitted to the Affiliated Hospital of Nantong University from July 2017 to July 2021 were selected. Among them, 99 cases treated by GLIM + SITA were assigned to the research group (RG) and 90 cases receiving GLIM monotherapy were set as the control group (CG).

The RG was composed of 59 males and 40 females, with a mean age of (48.08±9.64) years and a disease course of (7.73±1.06) years. There were 49 males and 41 females in the CG, with a mean age of (47.39±7.13) years and a disease course of (7.65±1.02) years. RG and CG were non-significantly different in general data (P>0.05), indicating clinical comparability. Ethical approval was obtained from The Affiliated Hospital of Nantong University.

Eligibility criteria

Treatment-naive patients (age: ≥18) were included, who met the diagnostic criteria for T2DM [15] and agreed to cooperate with the study, with normal communication and cognitive ability and no contraindications to GLIM or SITA.

Cases with severe liver and kidney function damage (with the liver and kidney function indexes exceeding the normal value by more than 1.5 times), drug allergies or mental illness were excluded, as were pregnant or lactating women.

Methods

Patients in the RG received the combination therapy of GLIM (Jiangxi Ruiweier Biotech, 93479-97-1) and SITA (Jiangxi Ruiweier Biotech, 486460-32-6), with the dosage of SITA being 100 mg/once a day and that of GLIM being 0.2 g/once daily. Cases in the CG were treated with GLIM monotherapy, the dosage of which was timely adjusted according to the BG dynamically measured. The initial dosage was 2 mg/once a day, with the maximum daily dosage no more than 6 mg. Both groups were treated for 3 months.

Response evaluation

Excellent: fasting blood glucose (FBG) decreased by more than 3.3 mmol/L.

Good: FBG decreased by 1.1-3.3 mmol/L.

Poor: non-compliance with the above criteria.

Outcome measures

Treatment outcomes: The Response evaluation section shows the evaluation criteria of excellent or good treatment. The excellent or good rate of treatment was the percentage of the total number of patients whose curative effect was evaluated as excellent or good divided by the total number of cases.

BG: FBG and 2-hour postprandial blood glucose (2hPG) were measured with an automatic biochemical analyzer, and HbA1c was determined by affinity column chromatography.

Table 1. Baseline data [n (%), mean ± SEM]

Factor	Control group (n = 90)	Research group (n = 99)	χ^2/t	P
Gender (male/female)	49/41	59/40	0.511	0.475
Average age (years old)	47.39±7.13	48.08±9.64	0.555	0.580
Course of disease (years)	7.65±1.02	7.73±1.06	0.528	0.598
BMI (kg/m^2)	22.80±2.85	23.06±3.12	0.596	0.552
Alcoholism (Yes/No)	55/35	62/37	0.046	0.830
Smoking (Yes/No)	50/40	58/41	0.177	0.674
Hypertension (Yes/No)	47/43	53/46	0.033	0.857
Hyperlipidemia (Yes/No)	38/52	34/65	1.241	0.265

Note: BMI, body mass index.

Table 2. Impact of glimepiride plus sitagliptin on the treatment outcome of diabetic patients [n (%)]

Group	n	Excellent	Good	Poor	Excellent or good rate (%)
Control group	90	22 (24.44)	40 (44.44)	28 (31.12)	62 (68.88)
Research group	99	49 (49.49)	38 (38.38)	12 (12.13)	87 (87.87)
χ^2 value	-	-	-	-	10.189
P value	-	-	-	-	0.001

Islet function: The patients' fasting insulin (FINS) was detected by an automatic immune analyzer, and the Homeostasis Model Assessment of β-cell function (HOMA-β) and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) were calculated as follows: HOMA-β = 20 × FINS/(FBG-3.5), HOMA-IR = (FINS × FBG)/22.5.

OS: Malondialdehyde (MDA; Shanghai Huzhen Industrial Co., Ltd., HZ-E16657) and glutathione peroxidase (GSH-PX; Shanghai Westang Biotech, F00942) were detected by double-antibody sandwich enzyme-linked immunosorbent assay (ELISA), and superoxide dismutase (SOD; Shanghai Yuduo Biotech, YDLC-12748) was detected by the pyrogallol method.

IRs: ELISAs were performed to determine tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-18 concentrations. The experimental steps strictly followed the instructions of the corresponding ELISA kits (Shanghai Yuanmu Biotech, YM-SZ0122, YM-SZ0049, YM-SZ0049).

Safety: The incidences of adverse reactions such as hypoglycemia and digestive tract reaction were recorded.

Statistical processing

Data analysis was carried out by SPSS22.0. χ^2-test was used for comparison of counted data (represented by number of cases/percentage [n/%]). Independent samples t-test was adopted to analyze inter-group differences of measured data (represented by mean ± SEM) and paired t-test to identify intra-group differences before and after treatment. P<0.05 was used as the significance level.

Results

Baseline data

The analysis of patients' baseline data (**Table 1**) revealed no statistical significance in gender, average age, disease course, body mass index (BMI), alcoholism, smoking, hypertension or hyperlipidemia between RG and CG (all P>0.05), suggesting comparability.

Impacts of GLIM plus SITA on diabetic patients

Efficacy assessment was conducted to analyze the impacts of GLIM plus SITA on the treatment outcome of diabetic patients (**Table 2**). The results showed an excellent or good rate of treatment of 87.87% in RG, significantly higher than that of 68.88% in CG (P<0.05).

Impacts of GLIM plus SITA on BG in diabetic patients

We detected BG indexes FBG, 2hPG, and HbA1c of patients to compare and analyze the impacts of the two medication regimes on BG of diabetic patients (**Figure 1**). The above BG indexes differed insignificantly between groups prior to treatment (P>0.05). However, the post-treatment FBG, 2hPG, and HbA1c of both groups decreased statistically and were lower in the RG compared to the CG (P<0.05).

Impact of GLIM plus SITA on islet function in diabetic patients

We detected islet β cell function indicators such as HOMA-β and HOMA-IR to analyze the

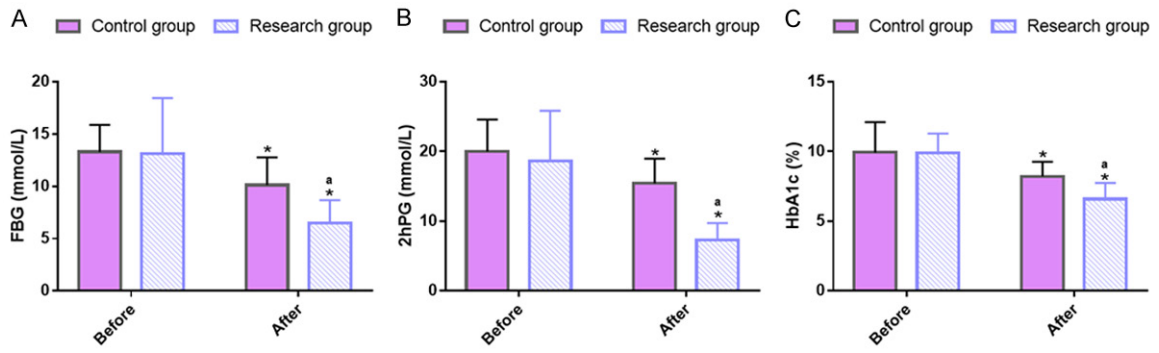

Figure 1. Blood glucose of diabetic patients. A. FBG of diabetic patients. B. 2hPG of diabetic patients. C. HbA1c of diabetic patients. Note: * represents P<0.05 compared to the level before treatment; "a" represents P<0.05 compared to the control group. FBG, fasting blood glucose; 2hPG, 2-hour postprandial blood glucose; HbA1c, glycosylated hemoglobin.

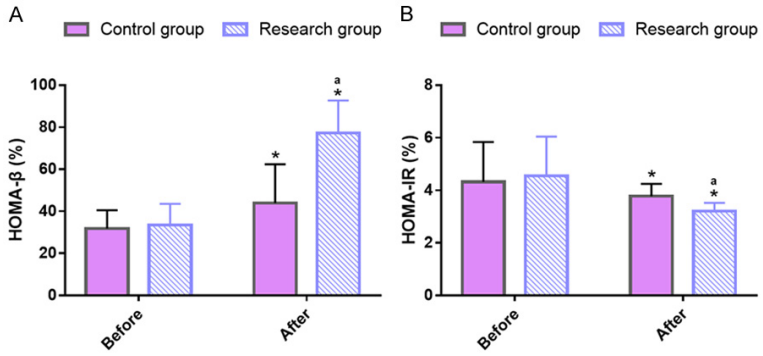

Figure 2. Islet function in diabetic patients. A. HOMA-β in diabetic patients. B. HOMA-IR in diabetic patients. Note: * represents P<0.05 compared to the level before treatment; "a" represents P<0.05 compared to the control group. HOMA-β, Homeostasis Model Assessment of β-cell Function; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance.

effects of the two intervention methods on islet function in diabetic patients (**Figure 2**). The results showed no significant difference in the islet β-cell function indexes between groups before treatment (P>0.05); while significantly increased HOMA-β and decreased HOMA-IR were observed in both groups after treatment (P<0.05). Compared to the CG, HOMA-β was higher and HOMA-IR was lower in the RG (P<0.05).

Impacts of GLIM plus SITA on OS in diabetic patients

We tested OS indexes (MDA, SOD, and GSH-PX) to evaluate the effects of the two treatments on OS in diabetic patients (**Figure 3**). Similarly, these OS indicators showed little differences between the RG and CG prior to treatment (P>0.05) and were altered to varying degrees after treatment (P<0.05). There were significant differences in their post-treatment levels between the RG and CG (P<0.05).

Impacts of GLIM plus SITA on IRs in diabetic patients

ELISAs were performed to test serum TNF-α, IL-6, and IL-18 of the two cohorts of diabetic patients, to evaluate the impacts of the two interventions on patients' IRs (**Figure 4**). The results also revealed no difference in the above three IFs between groups prior to intervention (P>0.05). The post-treatment levels of these IFs were markedly reduced (P<0.05) in both groups and were lower in the RG versus the CG (P<0.05).

Influence of GLIM plus SITA on the safety of diabetic patients

Lower incidences of hypoglycemia and gastrointestinal reactions were determined in the RG as compared to the CG, but the difference was not significant (P>0.05, **Table 3**).

Discussion

Type 2 diabetes (T2DM) is brought on by overweight, the aging process, hyperlipidemia, and other influences [16]. T2DM patients mainly

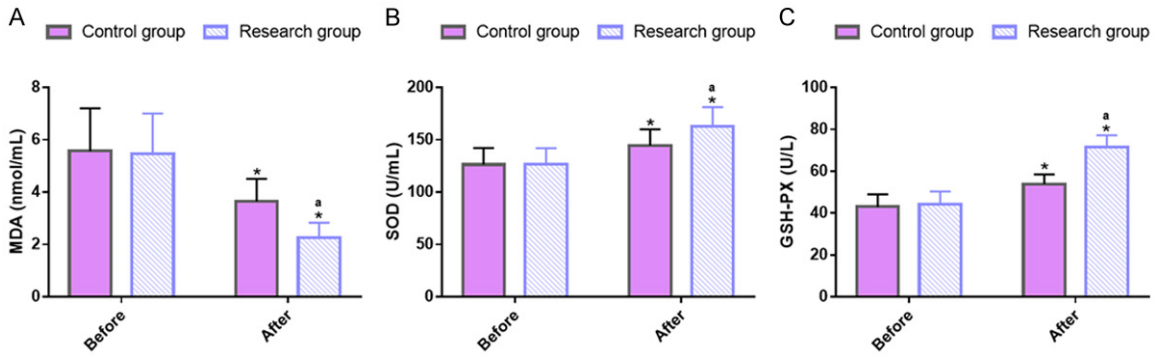

Figure 3. Oxidative stress in diabetic patients. A. MDA in diabetic patients. B. SOD in diabetic patients. C. GSH-PX in diabetic patients. Note: * represents P<0.05 compared to the level before treatment; "a" represents P<0.05 compared to the control group. MDA, malondialdehyde; SOD, superoxide dismutase; GSH-PX, glutathione peroxidase.

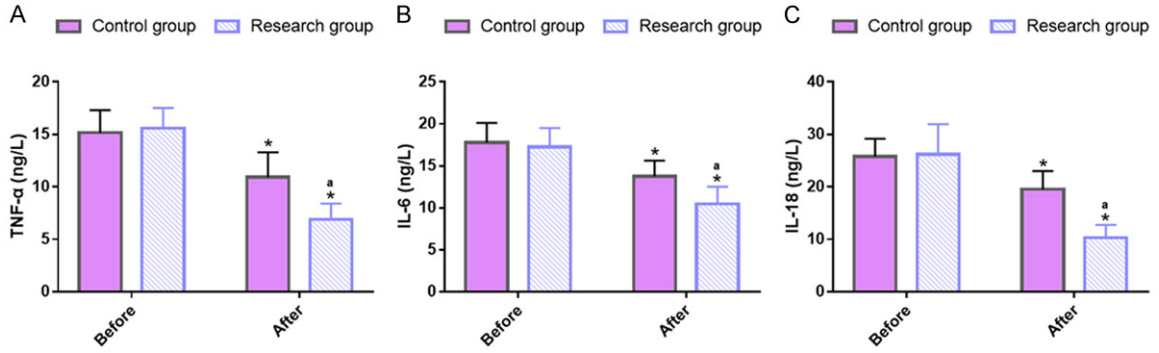

Figure 4. Inflammatory markers in diabetic patients. A. TNF-α in diabetic patients. B. IL-6 in diabetic patients. C. IL-18 in diabetic patients. Note: * represents P<0.05 compared to the level before treatment; "a" represents P<0.05 compared to the control group. TNF, tumor necrosis factor; IL, interleukin.

Table 3. Influence of glimepiride plus sitagliptin on the safety of diabetic patients [n (%)]

Category	Control group (n = 90)	Research group (n = 99)	χ^2 value	*P* value
Hypoglycemia	5 (5.56)	4 (4.04)	-	-
Gastrointestinal reaction	9 (10.00)	8 (8.08)	-	-
Total incidence	14 (15.56)	12 (12.12)	0.469	0.494

present with polyuria, fatigue, polydipsia, and blurred vision, which seriously affect their daily living and quality of life [17]. Therefore, in-depth analysis of the treatment strategies for T2DM patients and finding effective treatment strategies are of great value in improving their quality of life.

We studied the use of glimepiride (GLIM) plus sitagliptin (SITA). An animal study showed that GLIM exerted hypoglycemic effects by significantly reducing serum non-esterified fatty acids (NEFA) levels in T2DM rats, while SITA prevented vascular complications by exerting anti-inflammatory and endothelial repair effects [18]. GLIM can play a hypoglycemic role through a variety of mechanisms. One is to stimulate insulin secretion by binding to sulfonylurea receptors (SUR1) on pancreatic β cells, thereby inhibiting the glucose-dependence of K+ channels and contributing to their closure [19]. In addition, it can exert hypoglycemic action outside the pancreas by regulating physiologic processes such as peripheral glucose intake and insulin sensitivity, and inhibiting endogenous glucose production [20]. SITA also improves pancreatic β cell function and restores blood glucose (BG) levels by enhancing the active form of incretin [21]. Our research identified a significantly higher excellent or

good rate of treatment in the research group (RG) compared to the control group (CG) (87.87% VS 68.88), suggesting markedly better efficacy of GLIM + SITA for diabetic patients compared to GLIM monotherapy. Terauchi et al. [22] showed that SITA was as effective as GLIM in elderly patients with T2DM, but it contributed to a significantly lower incidence of non-severe hypoglycemia. Other evidence has shown that SITA is significantly more effective than GLIM in patients with T2DM, mainly reflected by better glycemic control with the former [23]. The post-treatment BG, FBG, 2hPG, and HbA1c in the RG were significantly lower than those before treatment and in the CG, indicating a significantly better recovery of abnormoal BG from the combined medications compared to the single medication. SITA is generally well tolerated and can improve the BG level and alleviate pancreatic β-cell dysfunction in T2DM patients with poor glycemic control under GLIM therapy [24]. A study by Chwieduk et al. [25] also confirmed that SITA had good performance in glycemic control in T2DM patients treated with GLIM with or without metformin intervention. Furthermore, we observed higher HOMA-β and lower HOMA-IR in the RG compared to the CG after intervention, suggesting that the combined intervention had a better effect improving β-cell function indexes. In the study by Saad et al. [18], both GLIM and SITA had inhibitory effects on HOMA-IR in HFD/STZ diabetic rats when used alone, which was similar to our findings.

Further, we evaluated the impacts of the two interventions on oxidative stress (OS) and the inflammatory response (IR). SOD and GSH-PX are antioxidant factors, while MDA is an index of peroxidation. All the three are involved in the process of OS, and the enhancement of antioxidant capacity can help improve the function of pancreatic β cells [26]. In addition, excessive secretion of TNF-α, IL-6, IL-18 and other pro-inflammatory indicators can lead to pancreatic β cell apoptosis, further aggravating the progression of diabetes [27]. Our results showed that MDA in the RG was significantly reduced after treatment and lower than in the CG, while SOD and GSH-PX were increased and higher, suggesting that combined drug intervention can significantly reduce OS in diabetic patients. Also, inflammatory indexes TNF-α, IL-6, and IL-18 in the RG were significantly lower after treatment than those before treatment and in the CG, indicating that GLIM + SITA has a significantly better inhibitory effect on patients' IRs than single drug therapy. In the study of Li et al. [28], GLIM reduced OS and inflammation in T2DM patients by significantly reducing the levels of 8 iso-prostaglandin F2α (8-iso-PGF2α), TNF-α and IL-6, similar to our research results. Nomoto et al. [29] also demonstrated that SITA may relieve the inflammation and OS in T2DM patients without advanced atherosclerosis. In terms of safety, we found no significant difference in the incidence of hypoglycemia and gastrointestinal reactions between the RG and the CG. This suggests that using the two drugs together is safe and does not significantly increase the incidence of adverse reactions In the study by Kobayashi et al. [30], patients treated with SITA had less common gastrointestinal diseases and comparable levels of hypoglycemia compared to alpha-glucosidase inhibitors (αGI), which is consistent with our findings. Similarly, the combination of SITA and metformin was reported as not significantly different from the combination of GLIM and metformin in terms of BMI changes and the risk of hypoglycemia, suggesting a comparable safety profile of the two combinations [31].

The innovation of this study is to confirm the clinical efficacy of GLIM + SITA in the treatment of T2DM patients from the aspects of efficacy, BG, islet function, OS, inflammatory indicators, and safety. The combination of the two drugs can improve patients' islet function and BG levels by regulating islet β-cell function indexes, safely contributing to better improvement of OS and inflammation than GLIM monotherapy. However, the following limitations of this study need to be addressed. First of all, the sample size of the two groups in this study was less than 100. This small sample size may have influenced the accuracy of the experimental results. Second, basic research will be needed to reveal the therapeutic mechanism of the combined medications. We will start with these points in the future to improve the research.

Conclusion

To sum up, GLIM plus SITA is superior to GLIM monotherapy in the treatment of diabetic patients. It contributes to significantly improved BG and effectively alleviates OS and IRs in

patients, with higher efficacy while maintaining safety. This may be a reliable new choice for the treatment of diabetic patients.

Disclosure of conflict of interest

None.

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