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Effect of Sitagliptin *Versus* Glibenclamide on Glycemic Markers, Lipid Profile Inflammatory and Oxidative Stress Factors in Type 2 Diabetes Patients: a Double-Blinded Randomized Controlled Trial

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ABSTRACT

Objectives: *Diabetes mellitus is leading to chronic complications, including cardiovascular diseases. The aim of this study was to compare the effect of Sitagliptin and Glibenclamide on glycemic markers, lipid profile inflammatory, and oxidative stress factors in type 2 diabetes patients.*

Methods: *This double-blinded randomized controlled trial was performed on patients with type 2 diabetes mellitus (n=54). The treatment group (27 patients) received 100 mg of Sitagliptin once daily + 500 mg Metformin twice daily, orally, for 12 weeks, and the control group (27 patients) was given 5 mg of Glibenclamide once daily + 500 mg Metformin twice daily, also orally, for 12 weeks. Serum levels of tumor necrosis factor alpha (TNF-α), high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), lipid profile [cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglyceride (TG)], fasting blood sugar (FBS) and hemoglobin A1C (HbA_{1c}), body weight, and body mass index (BMI) were measured before and after the study.*

Results: *In both groups, the FBS level was significantly reduced from baseline (P=0.03 in the Sitagliptin group and P=0.02 in the Glibenclamide one). The percent of HbA_{1c} was also significantly reduced from baseline in both the Sitagliptin group (P=0.01) and the Glibenclamide one (P=0.008). However, comparing the groups, these changes were not different. In the Sitagliptin group, IL-6 was significantly reduced from baseline (P=0.01) as well as in comparison with the Glibenclamide group (P=0.001). The TG level was significantly lower than the baseline in the Sitagliptin group (P=0.03), so changes between groups were*

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significant (P=0.04). Weight and BMI were significantly increased from baseline in the Glibenclamide group (P=0.02 and P=0.03, respectively), and their changes between the two groups were also significant (P=0.001).

Conclusions: *These finding support the favorable effects of Sitagliptin on cardiovascular risks beyond its advantages on insulin-glucose hemostasis in patients with type 2 diabetes.*

Keywords: Sitagliptin, Glibenclamide, type 2 diabetes mellitus, inflammation, FBS.

INTRODUCTION

Diabetes is an epidemic life-long disease which is associated with a considerable economic burden on healthcare systems globally (1). Type 2 diabetes is mainly recognized by hyperglycemia on the basis of decreased ability of β-cells to produce insulin or increased insulin resistance contributing to a set of metabolic disorders (1). Insulin resistance in diabetic patients is associated with an abnormal metabolism of carbohydrate, fat and protein, leading to hypertension, higher TG level and lower HDL, which are risk factors for microvascular, macrovascular and neuropathic diseases (2-4). Microangiopathic and glucose instabilities in diabetic patients can result in oxidative stress and inflammation by ROS production (2, 5). Overproduction of ROS leads to mitochondrial dysfunction and a reduced production of ATP (1). These conditions are considered as a main risk factor cardiovascular disease (CVD) (6), which is the most important cause of death and serious complications in patients with type 2 diabetes mellitus (T2DM) (7-9).

Therefore, proper management for controlling hyperglycemia is of great significance to hinder diabetes progression towards cardiovascular complications and other side effects (2). Thus, antidiabetic drugs that have protective effects on heart health would be an appropriate choice for patients with diabetes.

Metformin is respected as the prior choice in patients with type 2 diabetes, according to the Food and Drug Administration of America (FDA) guideline, while it fails to control the glucose level in 50% of patients as a sole remedy during period of three years. Therefore, prescribing adjuvant in combination with Metformin is an essential approach (10).

Dipeptidyl-peptidase-4 (DPP-4) inhibitors are considered an anti-hyperglycemic type of medication, which has been recently widely used. DPP-4 enzymes by metabolizing incretins can inactivatee glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP), leading to increasing insulin secretion, decreasing glucagon, and control glucose fluctuation (11). Sitagliptin is a common DPP-4 inhibitor used alone or in combination with other medications. Its prominent features in comparison with those of other DPP-4 inhibitors, including longer half-live, higher oral bioactivity, and higher selectivity, make it an exceptional choice. In addition, it is indicated as a safe medication without any considerable drug-drug interaction and severe adverse effects (10). Moreover, its valuable effects on cardiovascular disease (CVD) and microvascular complications have revealed a bright prospect in patients with diabetes who suffer from CVD (10). It has been asserted that sitagliptin can restore cardiac function, improve ejection fraction (EF) and fractional shortening (FS) (6).

Another antihyperglycemic medication is Glibenclamide, a KATP channel blocker belonging second-generation of sulfonylurea which triggers insulin secretion from pancreatic beta cells, as a result, blood glucose decrease (12, 13). Using Glibenclamide in combination with Metformin induces more promising effects in controlling blood glucose levels and also the lipid profile (14).

Therefore, this study aimed to compare the effect of sitagliptin and Glibenclamide on cardiovascular risk factors, including inflammatory markers (hs-CRP, IL-6 and TNF-α), lipid profile, glycaemic indexes, blood pressure and anthropometric features in patients with type 2 diabetes. ❑

METHODS

Study design and patients' characteristics

This is a double-blinded randomized controlled trial that conformed to the declaration of Helsinki and Good Clinical Practice Guidelines. The ethics committee of Ahvaz University of

Medical Sciences in Iran reviewed and approved the study protocol (approval number. IR.AJUMS. REC. 1394.281). This study was registered in the Iranian Registry of Controlled Trial (IRCT) (Number: IRCT2015102824768N1), where the trial protocol could be accessed. Written informed consent was obtained from each eligible participant.

All eligible patients had type 2 diabetes and were referred to Golestan Hospital, a clinic affiliated with Ahvaz University of Medical Sciences, Ahvaz, Iran, with health care providers including nurses, nutritionists, endocrinologist, and physicians.

Only type 2 diabetes patients aged 30-60 years, who were taking Metformin and had serum HbA_{1c} levels of 7.5–9 % and a duration of type 2 diabetes less than 10 years, were included in the present study. Patients with a history of anti-inflammatory and antihypertensive medications (such as NSAIDs, corticosteroids, ASA, estrogen, Tamoxifen), those who have been using a DDP-4 inhibitor over the past three months, or antihyperglycemic medication other than Metformin, or nitrate therapy, smoker patients and those with hypo- or hyper-thyroiditis, gastroparesis, heart failure, cancer, liver disease, pancreatitis, infectious diseases, pregnancy, lactation, uncontrolled blood pressure, inflammatory disease, and diabetic patients with anemia, GFR<60, and creatinine clearance below 30 mL /min were all excluded from the study.

Sample size

The sample size was determined based on TNF-α according to a previous study (15): 22 patients in each group, with a test strength of 80% and $\alpha=0.05$, mean difference of 2.6, standard deviation (SD) 1: 0.8, and SD 2: 0.4. To allow almost 20% drop out in each group, 27 patients per group were determined as the final sample size. A total of 54 patients with type 2 diabetes were screened and signed the informed consent participated in this trial.

Randomization

Participants were randomly assigned to two groups in a 1:1 ratio. Patients in the Sitagliptin group received 100 mg of Sitagliptin once daily and 500 mg Metformin twice daily, orally, for 12 consecutive weeks, while those in the Glibenclamide group received 5 mg of Glibenclamide once daily and 500 mg Metformin twice daily, also orally, for 12 consecutive weeks.

Random allocation software enabled patients' assignment using blocked randomization with a fixed block size of 4 and was done by an investigator who had no clinical contention in the trial. Other procedures, including enlistment, sequence generation, allocation concealment, and randomization process, were all accomplished by the principal investigators.

Intervention

When the FBS level was higher than 7.21 mmol/L, 2.5-5 mg of Glibenclamide per 5.55 mmol/L were added, and when it was lower than 3.88 mmol/L, the dose of Glibenclamide was reduced by 2.5 to 5 mg.

Outcome

Primary outcomes of this study were changes in TNF-α, hs-CRP, IL-6, and secondary outcomes included any changes in weight, BMI, blood pressure, lipid profile, FBS, and HbA_{1c}.

Before the study, the demographic questionnaires were filled through face-to-face interview by the main investigator. Blood samples in the fasting 12-hour period at the beginning and end of the intervention at Golestan hospital were collected by a laboratory expert nurse. Blood samples were centrifuged and serum was kept at -70°C in the freezer until final measurement for TNF-α, hs-CRP, IL-6, lipid profile, FBS, and HbA_{1c}

Measurement

The BMI was computed as the weight in kilograms divided by the height in meters squared. Blood pressure was measured twice, with an interval of at least five minutes, by a Mercury barometer (ALPK2). The mean of two measurements was considered as the subject's blood pressure. Plasma glucose levels, lipid profile and HbA_{1c} were assessed using an enzymatic colorimetric (GOD-PAP) methodology (Pars Azmoon Inc, Iran). Serum TNF-α and IL-6 levels were measured by Enzyme-linked Immunosorbent Assay (ELISA) (Diaclone, French) and Hs-CRP by Enzyme-linked Immunosorbent Assay (ELISA) (Zelbio, Germany) (16).

Statistical methods

Data were analyzed using SPSS software (Version 22; IBM, Armonk, USA). The normality of data

was evaluated by the Kolmogorov Smirnov test. To compare variations between the beginning and end of the intervention in each group, paired t-test was used for the data with normal distribution and Wilcoxon signed-rank test was used for skewed data. P<0.05 was considered significant. ❑

RESULTS

Eligible patients were recruited. During the treatment phase of the study, 10 patients left the study for different reasons (Figure 1).

There was no statistically significant difference between the baseline measured parameters among groups (Table 1).

In both groups, the FBS level was significantly reduced from baseline (P=0.03 in the Sitagliptin group and P=0.02 in the Glibenclamide one). However, comparing the groups, the changes were not different. The percent of HbA_{1c} was also significantly reduced from baseline in both the Sitagliptin group (P=0.01) and the Glibenclamide one (P=0.008); yet, the changes between the two groups for HbA_{1c} were not significant (Table 2).

In the Sitagliptin group, IL-6 was significantly reduced from baseline (P =0.01) and these changes were significant in comparison to the Glibenclamide group (P=0.001). The changes for hs-CRP and TNF-a were not significant between groups (Table 2).

The TG level was significantly lower than the baseline in the Sitagliptin group (P=0.03), so changes between groups were significant

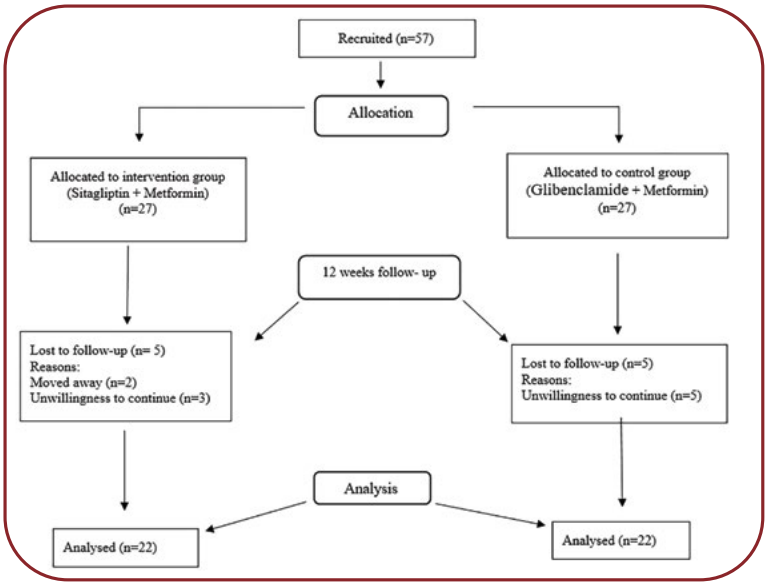

FIGURE 1. Flow diagram of the trial

	Intervention group (Sitagliptin + Metformin) (n=22)	Control group (Glibenclamide + Metformin) (n=22)	P-value*
Age (years)	48.3± 6.9	48.8± 6.4	0.77
Weight (kg)	82.17± 11.23	84.50± 14.89	0.36
BMI (kg/m^2)	28.68± 3.99	29.74± 4.29	0.36
FBS (mmol/L)	8.23±1.13	8.49 ± 1.28	0.79
A_{1C} %	7.68±0.27	7.74 ± 0.34	0.69
Cholesterol (mg/dL)	219.15±42.64	215.54± 30.18	0.97
LDL-C (mg/dL)	128.23±29.80	132.08± 25.01	0.61
HDL-C (mg/dL)	43.65±10.49	44.81± 8.29	0.66
Triglyceride (mg/dL)	209.27±106.34	196 ±76.18	0.60
IL-6 (pg/mL)	3.37±1.15	3.22± 0.92	0.63
TNF-α (pg/mL)	3.49± 1.42	3.60± 1.34	0.43
Hs-CRP (pg/mL)	2.51± 1.18	2.67± 1.51	0.34
DBP (mm Hg)	84. ±1 8.4	83.3± 7.2	0.39
SBP (mm Hg)	133.6± 9.9	129.6± 14.3	0.71

TABLE 1. Baseline demographic characteristics and measured parameters in patients

Note: Values for continuous variables, as mean _ standard deviation with normal distribution.
Baseline parameters are compared using one-way ANOVA.
P < 0.05 is considered significant.
BMI=body mass index; FBS=fasting blood sugar; A_{1C}=hemoglobin A_{1C}; LDL-C=low density lipoprotein cholesterol; HDL-C=high density lipoprotein cholesterol; IL-6=interleukin 6; TNF-α=tumor necrosis factor alpha; Hs-CRP=high- sensitivity C-reactive protein; DBP=diastolic blood pressure; SBP=systolic blood pressure.

TABLE 2. Baseline demographic characteristics and measured parameters in patients

Measured parameter	Sitagliptin + Metformin group (n=22)		Glibenclamide + Metformin group (n=22)		P-value[b]
	Changes	P-value[a]	Changes	P-value[a]	
Weight (kg)	-1.06±0.51	0.11	+1.10±1.52	0.02*	**0.001***
BMI (kg/m^2)	-0.12±0.19	0.21	+0.35±0.44	0.03*	**0.001***
FBS (mmol/L)	-0.75± 1.87	0.03*	-0.65±1.68	0.02*	**0.56**
A_{1C} %	-0.74±1.12	0.01*	-0.92±1.21	0.008*	**0.08**
Total cholesterol (mg/dL)	-13.31±8.98	0.39	-11.76±9.51	0.27	**0.78**
LDL-C (mg/dL)	-3.19±5.22	0.12	-6.66±5.74	0.39	**0.17**
HDL-C (mg/dL)	+2.13±3.89	0.32	+1.55±2.54	0.40	**0.11**
Triglyceride (mg/dL)	-14.43±23.74	0.03*	-10.96±5.14	0.06	**0.04***
IL-6 (pg/mL)	-0.84±1.03	0.01*	-0.75±0.21	0.63	**0.001***
TNF-a (pg/mL)	-0.51±0.14	0.49	-0.45±0.08	0.81	**0.21**
Hs-CRP (pg/mL)	-1.23±0.72	0.08	-1.05±0.61	0.09	**0.09**
DBP (mm Hg)	-1.31±0.68	0.24	-1.76±0.51	0.27	**0.48**
SBP (mm Hg)	-1.19±0.92	0.22	-1.66±0.84	0.32	**0.37**

NOTE: Data are expressed as mean _ standard deviation.
Measured parameters are compared using one-way ANOVA.
P < 0.05 is considered significant.
*: P-value < 0.05
P-value[a]: P-value within groups
P-value[b]: P-value between groups
BMI=body mass index; FBS=fasting blood sugar; A_{1C}=hemoglobin A_{1C}; LDL-C=low density lipoprotein cholesterol; HDL-C=high density lipoprotein cholesterol; IL-6=interleukin 6; TNF-α=tumor necrosis factor alpha; Hs-CRP=high-sensitivity C-reactive protein; DBP=diastolic blood pressure; SBP=systolic blood pressure.

(P=0.04). There was not any significant change for LDL-C, HDL-C and cholesterol within and between groups (Table 2).

Weight and BMI did not have any significant change from baseline in the Sitagliptin group; however, they were significantly increased in the Glibenclamide group (P=0.02 and P=0.03, respectively). The weight and BMI changes between the two groups were significant (P =0.001) (Table 2).

Systolic and diastolic blood pressure did not change in any of the two groups (Table 2). ❑

DISCUSSION

The present study showed that both Sitagliptin and Glibenclamide were effective in reducing FBS and HbA_{1c} in patients with type 2 diabetes. However, the significant reduction in inflammation and TG just were observed in the Sitagliptin group, without any significant increase in body weight and BMI.

Controlling blood glucose in type 2 diabetes patients is of great significance to attenuate microvascular diseases related to diabetes (17). Although many antidiabetic medications have been examined in patients with diabetes, their cardiovascular safety has not certainly confirmed (17).

The results of the present study showed that Sitagliptin and Glibenclamide were effective in controlling blood glucose and HbA_{1c} levels in patients with type 2 diabetes, which was consistent with many other studies (18-22).

DPP-4 inhibitors have been considered a somewhat new approach for type 2 diabetes patients and are recognized as second-line treatments for those with uncontrolled blood glucose after treatment with Metformin and lifestyle modifications, according to 2016 American Association of Clinical Endocrinologists (AACE), 2015 American Diabetes Association (ADA) and European Association of Clinical Endocrinologists (EASD) guidelines (23). DPP-4 inhibitors have the potential to control hyperglycemia (24) by decreasing fasting and postprandial glucose (25). The mechanism of action is throughout prolonging the action of GLP-1 and GIP leading to an increase in the action time of these two hormones in stimulating pancreatic cells (17, 25). In addition, DPP-4 inhibitors can lower HbA_{1c} levels as

strongly as other antidiabetic agents, while they do not have any typical adverse effects related to other antihyperglycemic medication, including hypoglycaemia, weight gain, gastrointestinal side effects. Besides, they are easy to use, with few exceptions (26). Among the different available types of DPP-4 inhibitors, Sitagliptin and Vildagliptin have been shown as the prior choice due to their greater therapeutic effects on HbA_{1c}, blood lipids and body weight, improving β-cell dysfunction and insulin resistance in patients with T2DM (23). Based on other studies Sitagliptin in the form of monotherapy or adjuvant therapy with metformin have potential effects on lowering blood glucose and HbA_{1c} (27-29).

Sulphonylureas are other antihyperglycemic agents exerting their beneficial effects by attaching to the sulphonylurea receptor (SUR)-1 subunit in ATP-sensitive potassium (KATP) channels of pancreatic β–cell, which results in closing this channel, depolarization of membrane of calcium channels (opens voltage-dependent type), leading to elevating intracellular calcium. High concentration of intracellular calcium allows insulin secretion into the blood circulation to control blood glucose (26). Hypoglycemia is the main adverse effect of these families (26). Complementary effects of sulfonylurea have also been observed when used concomitantly with Metformin. Since one leading to increased insulin secretion and the other leading to increased insulin sensitivity, their combination has been shown to be an appropriate choice in type 2 diabetes patients, which may have impaired both of these pathways (30).

Chronic inflammation and oxidative stress are well-known risk factors for cardiovascular disease, which strongly are associated with diabetes and obesity (31). Increasing inflammatory cytokines such as IL-6 plays an important role in the occurrence of long-term complications such as cardiovascular events in patients with type 2 diabetes (32). Inflammation not only plays an important role in altering vascular function in diabetic patients, but also can control many metabolic pathways by affecting the function of visceral adipose tissue as one of the important actors in the production of endocrine mediators (33). In our study, IL-6, an important inflammatory marker in the body, was significantly decreased after the administration of Sitagliptin compared with Glibenclamide. In line with our findings, a study conducted by Dobrian *et al* on obese mice showed that Sitagliptin could downregulate gene expression of inflammatory mediators including IL-6, TNF-α and IL-12 in adipose tissue as well as decreased expression of MCP-1, IL-6, IL-12, and IP-10 in Islet cells of the endocrine system (33). Derosa *et al* examined the changes in inflammatory biomarkers after Sitagliptin treatment in patients with type 2 diabetes that were not controlled with metformin; they found that the Sitagliptin group was more effective in controlling blood sugar than the placebo group; also, a decrease in the level of inflammatory biomarkers was observed (34). Another study also showed the effect of 100 mg/day Sitagliptin on improving IL-6 and IL-8 after 12 weeks of intervention in patients with type 2 diabetes (32). Asahara *et al* revealed that 50 mg/day Sitagliptin decreased hs-CRP and TNF-a and increased IL-10 in patients with type 2 diabetes (15). In a study that evaluated the effects of administrating Sitagliptin on β-cell function and various inflammatory biomarkers in type 2 diabetes patients and treatment with Sitagliptin + Metformin, TNF-α levels were significantly decreased after nine months (35).

Sitagliptin is supposed to have a role in reducing inflammatory cytokines by elevating GLP-1 levels (36). These anti-inflammatory effects are probably mediated by phosphorylation JAK2 and STAT3 and therefore, downregulation of the JAK/STAT pathway, which is correlated with a lower level of cardiac IL-6 and improving cardiac hypertrophy (37). Also, by modifying postprandial lipoprotein, Sitagliptin can downregulate proinflammatory gene expression and attenuate inflammation in endothelial cells, leading to an improvement of the endothelial function (36). Besides, some studies that investigated the effect of Sitagliptin on TNF-a throughout NUR77 gene promoter regulation proposed that Sitagliptin was more likely to have an anti-atherosclerotic effect by decreasing ICAM-1, VCAM-1 and PAI-1 in a GLP-1-dependent manner (38).

Sitagliptin has been shown to have attenuating effects on lipid accumulation (10). Comparing the effects of the two studied drugs on the blood lipid profile indicated that treatment with Sitagliptin resulted in a significant decrease in blood TG levels when compared with Glibenclamide. In line with our study, Lea Duvnjak *et al* revealed that a three-month intervention with 100 mg/day Sitagliptin reduced serum cholesterol, LDL-C and TG level in T2DM patients (39). The study of Mazhar

Hussain revealed a lower level of serum cholesterol, LDL and TG, and a higher level of HDL-C in non-diabetic patients treated with 100 mg/day Sitagliptin for three months (40). It was also found by another study that when Sitagliptin was added to Metformin in type 2 diabetes patients, it resulted in a slight but statistically significant decrease in total blood cholesterol and TG levels (41). The effects of different GLP-1 agonists such as exenatide and liraglutide on improving lipid profiles have also been demonstrated (42-45).

Incretin hormones such as GLP-1 can improve hyperlipidaemia by delaying gastric emptying. GLP-1 secretion increases in response to eating a meal by the intestine and by inserting its effect on pancreatic β-cells and insulin secretion modify the postprandial blood glucose level and diminish plasma free fatty acids (FFAs) by inhibiting lipolysis in the adipose tissue. Also, GLP-1 can decrease VLDL production through direct effects on the liver and by suppression of apoB-48 and CM biogenesis in the gut through both direct and indirect effects, such as reducing lymph flow, repressing gastric emptying and preventing gastric lipase. Thus, postprandial lipidemia can be regulated by DPP-4 inhibitor that prolong the activity of GLP-1 (46).

Glibenclamide-based treatment protocol increased the BMI, whereas the administration of Sitagliptin did not cause any significant change in patients' weight. The difference between the Glibenclamide-induced weight gain and the Sitagliptin-induced weight maintenance was significant between the two groups. The results of the present study are in line with those of other published studies, suggesting weight gain as a result of Glibenclamide consumption (31) compared to the beneficial effects of DPP-4 inhibitors in weight control and weight loss (47). Sitagliptin moderately delayed gastric emptying by inhibiting DPP-4 (48). As gastric emptying has an impact on body weight and on self-reported feelings of satiation (49), delayed gastric emptying caused by DPP-4 inhibitors could potentially improve hyperphagia. Moreover, DPP-4 inhibition may have an inhibitory effect on fat absorption from the gut and helps lipolysis in the adipose tissue in the postprandial state (50).

The effects of diabetes on endothelial dysfunction and arterial stiffness have been well established (51). Inducing the relaxation of arteries by GLP-1 has been reported by a previous study (52). A significant reduction in both systolic and diastolic blood pressure with different GLP-1 analogues has been shown by some large studies (53). Sitagliptin has been related to small but significant reductions in 24-hour ambulatory systolic and diastolic blood pressure compared with a placebo in hypertensive patients without diabetes (54). In the present study, in conflict with the earlier published data, a useful effect of GLP-1 analogues on blood pressure was not revealed. The lack of significance can be explained by the fact that patients in both groups did not have high blood pressure at baseline.

The present study had some limitations: firstly, the sample size was lower than that used in other studies, and secondly, some factors indicating oxidative stress and endothelial function were not measured. ❑

CONCLUSION

Both Sitagliptin and Glibenclamide are commonly used as second-line antidiabetic medication. Our study showed that they have similar effects on HbA_{1c} and FBS; however, Sitagliptin has also reduced the IL-6 level and TG and increased HDL-C. Moreover, it did not lead to any weight gain in our patients. Therefore, Sitagliptin is more likely to be a prior choice in diabetes patients with cardiovascular diseases since it has the potential to improve inflammation and lipid profile. These findings support the favorable effects of Sitagliptin on cardiovascular risks beyond its advantages on insulin-glucose hemostasis in patients with type 2 diabetes. ❑

Conflicts of interest: none declared.

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Authors' contributions: research idea and study design: JH and MZ; data acquisition: JH; data analysis/interpretation: JH; statistical analysis: HR, SBGH; supervision or mentorship: MZ, SPP.

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