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Comparative Study on Adding Pioglitazone or Sitagliptin to Patients with Type 2 Diabetes Mellitus Insufficiently Controlled With Metformin

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Abstract

BACKGROUND: Diabetes mellitus is a progressive disorder that often requires combination therapy.

AIM: This study aimed to compare and study of add-on sitagliptin versus pioglitazone in patients with type 2 diabetes inadequately controlled with metformin.

METHODS: This 12-week, randomised, open-label and single centre study compared sitagliptin (100 mg daily, n = 80) and pioglitazone (30 mg daily, n = 80) in type 2 diabetic patients whose disease was not adequately controlled with metformin.

RESULTS: The mean change in HbA1c from baseline was -1.001 ± 0.83 with sitagliptin and -0.75 ± 1.20 with pioglitazone, and there were no significant difference between groups (P = 0.132). The mean change in fasting blood sugar (FBS) was -18.48 ± 33.32 mg/dl with sitagliptin and -20.53 ± 53.97 mg/dl with pioglitazone, and there were no significant difference between groups (P = 0.773). Sitagliptin caused 1.08 ± 2.39 kg decrease in weight, whereas pioglitazone caused 0.27 ± 2.42 kg increase in weight, with a between-group difference of 0.81 kg (P < 0.001). On the other hand, in sitagliptin group, there was greater improvement in lipid profile than pioglitazone group.

CONCLUSION: Sitagliptin and Pioglitazone demonstrated similar improvements in glycemic control in type 2 diabetes mellitus patients whose diabetes had been inadequately controlled with metformin. Nevertheless, sitagliptin was more effective than pioglitazone regarding lipid and body weight change.

Introduction

Due to the progressive decline in the function of pancreatic beta cells and chronic insulin resistance in patients with type 2 diabetes mellitus (T2DM), hyperglycemia increases over time in this group of patients [1, 2]. Several studies have demonstrated that hyperglycemia is one of the major risk factors in the development of microvascular complications in T2DM patients [3, 4]. On the other hand, clinical trials have shown that reduction in HbA1c can decrease the development of T2DM complications [5, 6]. For instance, every one percent HbA1c decrease is associated with Thirty- five percent decrease in risk of microvascular complications [7]. American Diabetes Association (ADA) recommended lowering the HbA1c to less than 7% in T2DM patients [8, 9]. Due to the complex nature and multiple metabolic defects of this disease, treatment with a single oral antihyperglycemic agent is not sufficient for reaching the desired goal, hence combination drug therapy is usually required to manage patients with T2DM [6, 8, 10, 11]. It should be noted that combination therapy with oral drugs requires the use of anti-hyperglycemic drugs with different complementary physiologic mechanisms to improve glycemic control [12].

Moreover, Beta-cell failure occurs long before T2DM is diagnosed and by this time, diabetic subjects have lost over 80% of their beta cell function. So, early treatment with anti-hyperglycemic drugs in diabetic patients can have positive effects on the preservation of residual pancreatic beta cells function [7, 8].

America Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommend metformin as a first line drug in the treatment of diabetic patients, because metformin is inexpensive, does not cause weight gain, has proven safety records and probably beneficial effects on the cardiovascular system. Sulphonylureas, thiazolidinediones and dipeptidyl peptidase 4 (DPP-4) inhibitors have also been recommended as an alternative treatment or in combination therapy with metformin in the ADA/EASD consensus [4, 13].

Metformin is a drug that can reduce Hb1Ac by increasing liver and peripheral tissue sensitivity to glucose, prevent hepatic gluconeogenesis and glycogenolysis. This reduction in Hb1Ac is about 1.2-3%, but metformin does not prevent beta cell failure, and after an initial decrease, HbA1c rises progressively [7, 14, 15].

Pioglitazone is one of the thiazolidinediones. Thiazolidinediones are Peroxisome Proliferator-Activated Receptor γ (PPAR- γ) agonists and are appropriate for use as monotherapy and in combination with metformin and/or a sulphonylurea in patients with T2DM [16,17]. Thiazolidinediones can decrease insulin resistance by increasing the sensitivity of muscle, liver, and adipose tissue to insulin. These drugs delay the progression of T2DM and can improve beta cell function and create a sustainable reduction in Hb1Ac [7, 18, 19].

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that can affect the path of incretin hormones including Glucagon-Like Peptide 1 (GLP-1) and Glucose-dependent Insulin releasing Polypeptide (GIP). These hormones are secreted by the intestine endocrine cells in response to a meal. GLP-1 and GIP stimulate insulin secretion (in a glucose-dependent manner) and delay gastric emptying. Also, GLP-1 can affect pancreatic alpha cells and inhibit glucagon secretion. Within some minutes after the release of these hormones, GIP and GLP-1 undergo rapid metabolism to inactive metabolites by the enzyme DPP-4, hence sitagliptin by inhibiting this enzyme causes an increase in the duration of validity of hormones in the blood [2, 8, 10, 17].

As earlier mentioned, Metformin, Pioglitazone and sitagliptin each possess different but complementary mechanisms of action. Therefore, we can use these drugs together as a combination therapy [2, 12, 20].

The aim of the present study was to compare the efficacy of dual anti-hyperglycemic combination therapy in T2DM patients, to find the most efficient and effective method for treating these patients.

Materials and Methods

Study design

This open-label, single centre and randomised control trial (code: IRCT2015061619554N4) were done between January 2016 and January 2017 in vali-e-asr hospital under the approval of Zanjan Metabolic Disease Research Center (ZMDRC), Zanjan University of Medical Sciences.

This study was approved by the ethics committee of Zanjan University of Medical Sciences.

Patients

Eligible patients were men and women, 30-60 years of age with T2DM and inadequate glycemic control (HbA1c ≥8 and ≤9.5) while being actively treated with metformin. Their body mass index (BMI) was between 25-35.

Patients with an history of ketoacidosis, unstable or rapidly progressive diabetic retinopathy, nephropathy, neuropathy, impaired hepatic function (defined as plasma aminotransferase level three times higher than the upper limit of normal for age and sex), impaired renal function (defined as serum creatinine level higher than the upper limit of normal for age and sex), impaired digestive function (vomiting, diarrhea, dyspepsia), a serious cardiovascular disease with ejection fraction less than 35%, pregnant women, breastfeeding women and women planning for pregnancy were excluded. All patients provided written informed consent to participate in the study.

Treatment

One hundred and sixty (160) T2DM patients were randomly assigned in a 1:1 ratio to one of the following treatment groups by permuted block method using a central computer-based randomisation (Figure 1).

The first group: those treated with sitagliptin 100 mg/day in addition to their usual doses of metformin for 12 weeks.

The second group: those treated with pioglitazone 30 mg/day in addition to their usual doses of metformin for 12 weeks.

All the patients were trained on the diabetic regimen by the nutritionist. All the individuals were also advised to increase their physical activity. For example, 3 to 5 times per week and each time for 20 to 30 min walking briskly or cycling. Possible side effects of drugs were also explained to patients.

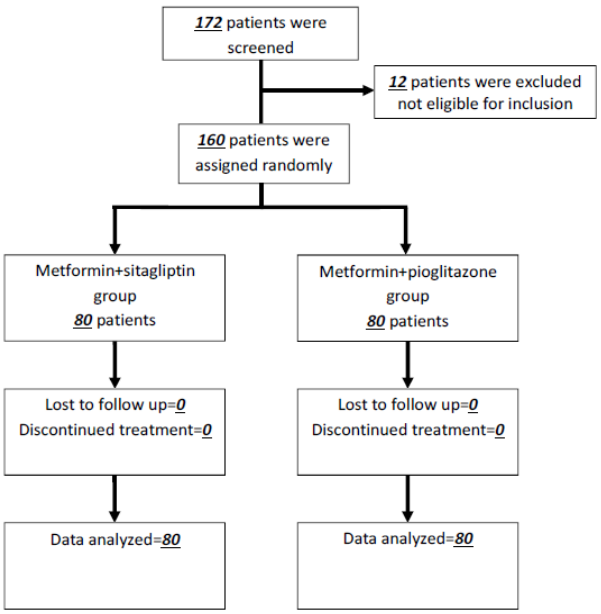

Figure 1: Study flowchart

Assessment

Before the study, all participants underwent an initial assessment that included FBS, Bs2hpp, HbA1c, Cholesterol, Triglyceride, HDL, BUN, Cr, AST and ALT in the laboratory of Vali-E-Asr Hospital. Blood pressure was measured using a manometer, weight by an analogue scale with an accuracy of 0.5 kg that was calibrated every day. Every month, the patients were followed regarding diet, physical activity, proper usage of drugs and side effects of drugs.

After three months FBS, BS2hpp, HbA1c, Chol, TG, HDL, BUN, Cr, AST and ALT were monitored in patients in the Vali-E-Asr Hospital central laboratory. Blood pressure and weight were also re-measured for each patient.

Statistical analysis

For collecting data, a questionnaire was designed in which demographic, anthropometric and the laboratory data were recorded. According to the results of the previous study that was reported, the mean change in HbA1c for sitagliptin and metformin groups were −0.86 (−1.02, −0.69) and −0.58 (−0.76, −0.40) respectively, the sample size was calculated with the power of 80% and two-sided type 1 error rate of 0.05 [13]. Therefore, At least 77 patients in each group were needed.

An intention-to-treat (ITT) analysis was performed for the 160 patients after randomisation, and statistical analysis was done using computer software SPSS version 18 (SPSS Inc, Chicago, IL, USA). The distribution of quantitative data was assessed using the Kolmogorov–Smirnov test. Treatment groups were compared using the Student's *t*-test for continuous variables. Comparison of only qualitative data (sex) was performed using Chi-square test. The differences in the changes of the HbA1c from 0–12 weeks were also determined using a multivariate analysis in which treatment groups were considered as predictor and age, sex, weight and lipid profile as covariates.

In this trial, results were presented as a mean ± standard deviation. A p value of < 0.05 was considered to be statistically significant.

Results

Demographic and baseline characters

One hundred and seventy-two patients whose diabetes had been inadequately controlled with metformin were screened for this trial. Twelve patients were excluded from the study because they did not meet the inclusion criteria. Therefore, 160 patients were randomly assigned to the metformin-sitagliptin or metformin-pioglitazone group. All of these patients completed the study (Figure 1). About 50% of patients were in the metformin plus sitagliptin group (Group 1) and 50% in the metformin plus pioglitazone group (Group 2). The mean age of Group 1 and Group 2 was 50.70 ± 7.85 and 55.12 ± 5.85, respectively. The percentage of female participants in the first group was 57.5% and in the second group was 71.3%.

Baseline variables in both groups are summarised in Table 1.

Table 1: Baseline parameters of the patients in each group

Variable	MEAN ± SD Group 1 (METFORMIN+SITAGLIPTIN)	Group 2 (METFORMIN+PIOGLITAZONE)	P value
Age (year)	50.70 ± 7.85	55.12 ± 5.85	<0.001
FBS (mg/dl)	171.09 ± 46.41	170.26 ± 56.14	0.919
BS2hpp (mg/dl)	276.80 ± 62.08	244.00 ± 77.73	0.004
HbA1c (%)	8.74 ± 0.60	8.63 ± 0.64	0.25
BUN (mg/dl)	10.30 ± 1.97	10.90 ± 3.25	0.16
Creatinin (mg/dl)	0.94 ± 0.16	0.95 ± 0.17	0.79
AST (U/L)	40.98 ± 37.52	27.81 ± 5.9	0.002
ALT (U/L)	40.89 ± 28.19	26.60 ± 6.42	<0.001
TG (mg/dl)	168.38 ± 80.76	176.74 ± 106.43	0.57
Chol (mg/dl)	177.00 ± 46.51	176.49 ± 35.98	0.93
HDL (mg/dl)	43.18 ± 8.38	43.95 ± 8.67	0.56
Weight (kg)	74.29 ± 13.62	73.01 ± 11.49	0.52
SBP (mmHg)	129.00 ± 18.18	121.81 ± 14.39	0.006
DBP (mmHg)	80.00 ± 9.27	69.88 ± 7.37	<0.001

FBS= fasting blood glucose; BS2hpp= two-hour blood glucose; HbA1c = glycosylated hemoglo- bin; BUN= blood urea nitrogen; AST = aspartate aminotransferase; ALT = alanine aminotransferase; TG = triglycerides; Chol= cholesterol; HDL = high-density lipoprotein; SBP= systolic blood pressure; DBP= diastolic blood pressure

HbA1C

Metformin-sitagliptin group (Group 1) and metformin-pioglitazone (Group 2) had similar baseline HbA1c level (Table 1). The mean HbA1c levels in the sitagliptin group ameliorated from 8.74 ± 0.60% to 7.74 ± 0.90% (p < 0.001) (Table 2). In the pioglitazone group, HbA1c improved from 8.63 ± 0.64% to 7.88 ± 1.2% (p < 0.001) (Table 3). The difference between the changes produced in the two groups was not

statistically significant (p = 0.132) (Table 4).

At the end, when the multivariate analysis to eliminate the confounding effects of other variables including age, sex, weight and lipid profile was conducted, no difference was detected between the two treatment groups in decreasing of HbA1c levels before and after treatment (β = 0.059, t = 0.360, P value = 0.719).

Table 2: The mean and standard deviation of variables in the study before and after treatment in the group treated with metformin and Sitagliptin (group 1)

Variable	MEAN ± SD		P value
	Before treatment	After treatment	
FBS (mg/dl)	171.09 ± 46.41	152.60 ± 42.33	<0.001
BS2hpp (mg/dl)	276.80 ± 62.08	228.29 ± 63.18	<0.001
HbA1c (%)	8.74 ± 0.60	7.74 ± 0.90	<0.001
BUN (mg/dl)	10.30 ± 1.97	10.18 ± 1.99	0.55
Creatinin (mg/dl)	0.94 ± 0.169	0.958 ± 0.15	0.48
AST (U/L)	40.98 ± 37.52	37.99 ± 23.55	0.78
ALT (U/L)	40.89 ± 28.19	38.14 ± 16.83	0.63
TG (mg/dl)	168.38 ± 80.76	133.98 ± 55.38	<0.001
Chol (mg/dl)	177.00 ± 46.51	153.31 ± 34.91	<0.001
HDL (mg/dl)	43.18 ± 8.38	46.35 ± 12.19	0.006
Weight (kg)	74.29 ± 13.62	73.2 ± 13.13	<0.001
SBP (mmHg)	129.00 ± 18.18	125.50 ± 13.20	0.025
DBP (mmHg)	80.00 ± 9.27	77.88 ± 7.41	0.012

FBS

The two treatment groups had comparable FBS at baseline (Table 1). The mean FBS levels in the sitagliptin group improved from 171.09 ± 46.41 to 152.60 ± 42.33 (p < 0.001) (Table 2). In the pioglitazone group, FBS improved from 170.26 ± 56.144 to 149.72 ± 46.66 (p < 0.001) (Table 3). The difference between the changes produced in the two groups was not statistically significant (p = 0.773) (Table 4).

BS2hpp

The mean changes in BS2hpp were −48.51 ± 57.13 mg/dl with sitagliptin and −31.51 ± 54.20 mg/dl with pioglitazone. The difference between the changes produced in the two groups was not statistically significant (P = 0.05) (Table 4).

Table 3: The mean and standard deviation of variables in the study before and after treatment in the group treated with metformin and pioglitazone (second group)

Variable	MEAN ± SD		P value
	Before treatment	After treatment	
FBS (mg/dl)	170.26 ± 56.144	149.72 ± 46.66	<0.001
BS2hpp (mg/dl)	244.00 ± 77.73	212.49 ± 66.56	<0.001
HbA1c (%)	8.63 ± 0.64	7.88 ± 1.20	<0.001
BUN (mg/dl)	10.90 ± 3.25	10.80 ± 2.67	0.54
Creatinin (mg/dl)	0.95 ± 0.17	1.005 ± 0.81	0.58
AST (U/L)	27.81 ± 5.90	27.60 ± 6.05	0.38
ALT (U/L)	26.60 ± 6.42	26.26 ± 6.80	0.231
TG (mg/dl)	176.74 ± 106.43	177.59 ± 86.79	0.937
Chol (mg/dl)	176.49 ± 35.98	171.50 ± 37.98	0.249
HDL (mg/dl)	43.95 ± 8.67	44.12 ± 8.28	0.823
Weight (kg)	73.01 ± 11.49	73.29 ± 11.50	0.314
SBP (mmHg)	121.81 ± 14.39	119.09 ± 14.01	0.06
DBP (mmHg)	69.88 ± 7.37	69.12 ± 7.78	0.397

Weight

A mean decrease in weight in Group 1 was 1.08 ± 2.39 kg from baseline after 12 weeks, and this change was statistically significant (p < 0.001) (Table 4). In contrast to this, subjects of Group 2 had a mean increase of 0.27 ± 2.42 kg in their weight from a baseline, which was not statistically significant (p = 0.314) (Table 4). The difference between the changes produced in the two groups was statistically significant (P < 0.001) (Table 4).

Lipid profile

The two treatment groups had comparable TG, chol and HDL at baseline (Table 1). The mean TG, chol and HDL levels in the sitagliptin group improved from 168.38 ± 80.76 to 133.98 ± 55.38 (p < 0.001), 177.00 ± 46.51 to 153.31 ± 34.91 (p < 0.001) and 43.18 ± 8.38 to 46.35 ± 12.19 (p = 0.006) (Table 2), respectively. In the pioglitazone group, TG, chol and HDL levels changed from 176.74 ± 106.43 to 177.59 ± 86.79 (p = 0.937), 176.49 ± 35.98 to 171.5 ± 37.98 (p = 0.249) and 43.95 ± 8.67 to 44.12 ± 8.28 (p = 0.823), respectively (Table 3). The difference between the changes produced in the two groups regarding these parameters was statistically significant (Table 4).

Table 4: The mean and standard deviation of changes in baseline variables after intervention in both groups

Variable	MEAN ± SD		P value
	Group	Group	
	metformin+sitagliptin	metformin+pioglitazone	
FBS (mg/dl)	-18.48 ± 33.32	-20.53 ± 53.97	0.773
BS2hpp (mg/dl)	-48.51 ± 57.13	-31.51 ± 54.20	0.05
HbA1c (%)	-1.001 ± 0.83	-0.75 ± 1.20	0.132
BUN (mg/dl)	-0.125 ± 1.88	-0.10 ± 1.47	0.92
Creatinin (mg/dl)	0.01 ± 0.13	0.055 ± 0.80	0.66
AST (U/L)	-2.99 ± 14.90	-0.21 ± 2.29	0.105
ALT (U/L)	-2.75 ± 13.02	-0.34 ± 2.50	0.106
TG (mg/dl)	-34.40 ± 52.97	0.85 ± 96.60	0.005
Chol (mg/dl)	-23.66 ± 39.33	-4.98 ± 38.39	0.003
HDL (mg/dl)	3.17 ± 9.96	0.17 ± 6.99	0.029
Weight (kg)	-1.08 ± 2.39	0.27 ± 2.42	<0.001
SBP (mmHg)	-3.50 ± 13.69	-2.72 ± 12.75	0.71
DBP (mmHg)	-2.12 ± 7.41	-0.75 ± 7.87	0.25

Other biochemical parameters

The change in blood pressure, liver function tests and kidney function tests at the end of the study from baseline was not significant between two groups (*P* > 0.05) (Table 4).

Adverse effects

In our study, there was no significant side effect such as hypoglycemia, oedema of the extremities, gastrointestinal symptoms, liver complications, kidney complications, cardiac complications and eye complications including macular oedema in both combination treatment groups. Also, both metformin-sitagliptin and metformin-pioglitazone were well tolerated.

Discussion

In this study, sitagliptin with pioglitazone in T2DM patients whose diabetes had been inadequately controlled with metformin was compared. This study aimed to evaluate which agent is preferable to an additional non-insulin antidiabetic drug for patients who have been uncontrolled with metformin.

The results demonstrated that although metformin-sitagliptin and metformin-pioglitazone had a great impact on the reduction of HbA1c, there was no significant difference between two groups (P value = 0.132). The rate of reduction of HbA1c in metformin-sitagliptin and metformin- pioglitazone groups was 1.001 ± 0.83 and 0.750 ± 1.20 respectively, and the difference between two groups was 0.26. Sung-Chen Liu in Taiwan achieved HbA1c reduction in metformin-sitagliptin group as 0.71 ± 0.12 and in the metformin-pioglitazone group as 0.94 ± 0.12. The difference between two groups in this study was 0.23, and there was no statistically significant difference between them (P-value = 0.17) [21]. As can be seen, the response to treatment in this study was slightly better than Sung-Chen Liu's study. Part of this difference depends on the mean age of the participants in the two studies. The mean age in our study was 52.91 ± 7.25 and was about 60 years in Sung-Chen Liu's study. Old age can reduce the response to treatment. Older patients usually have a longer duration of diabetes and insulin resistance in elderly patients can be more when compared to younger patients [22, 23]. All of these factors can reduce the response to treatment. Chawla et al. also could not find any statistically significant difference in HbA1c reduction between these two treatment groups (P-value = 0.203) [24].

Takihata et al. in a study that was done in Japan compared these two recent combination therapy in T2DM patients [13]. In contrast with our results, they reported that in Japanese with type 2 diabetes mellitus, sitagliptin is much more effective than pioglitazone. Although in their study, the difference between two groups was statistically significant (P value = 0.024), this result can be attributed to the lower body weight of the subjects in this study in comparison with our study (66.9 kg against 73.65 kg). Also, it can also be attributed to the fact that Japanese T2DM patients have lower levels of insulin secretion and insulin resistance than other races [25, 26].

According to our results, reduction in FBS was statistically significant after intervention in both groups, but no statistically significant difference was observed between treatment groups (P-value = 0.773). Chawla and Takihata, in two separate studies in line with the results of our study, did not report any significant difference in the FBS between the two-drug combination [13, 24]. In contrast, Sung-Chen Liu reported that the combination therapy, metformin-pioglitazone is more effective than metformin-sitagliptin with relation to the decreased FBS from baseline to endpoint [21]. Studies suggest that the impact of pioglitazone on blood sugar is by improving hepatic and peripheral insulin resistance [19, 24]. Based on this fact and because the population in Sung-Chen Liu's study were older than our study, it, therefore, implies their resistance to insulin may be higher. In this condition and due to the mechanism of pioglitazone function, this reason can be expected. There are few studies in which the effect of these two combination therapies on BS2hpp is compared. In this trial, we concluded that metformin-sitagliptin combination is more effective on BS2hpp. Sitagliptin can improve both fasting and postprandial hyperglycemia effectively [27, 28, 29], but pioglitazone improves mainly fasting hyperglycemia [30]. So with this description, our results are expected.

As shown from the trial, weight gain is a well-known consequence of pioglitazone treatment, while weight neutrality has been observed in sitagliptin studies both in monotherapy and combination therapy settings [31, 32]. Overweight is associated with insulin resistance so that weight loss can lead to improvements in insulin resistance and thus better response to treatment [33, 34]. This implies that weight neutrality of sitagliptin may offer a great advantage in T2DM management.

It can also be seen that metformin-sitagliptin in comparison with metformin-pioglitazone resulted in a better improvement in lipid profile status. In treatment with sitagliptin, cholesterol and triglyceride showed more reduction and HDL showed more increase. In contrast with the results from this study, Takihata [13] and Chawla [24] could not find any significant difference between two treatment groups regarding lipid profile. Sung-Chen Liu reported the better effect of metformin- sitagliptin on triglyceride levels, but in this study, pioglitazone was more effective in increasing HDL levels [21]. Although to date, there is not enough evidence about the certain mechanisms that improve the lipid profile in patients treated with Sitagliptin [24, 35], part of the improvement in lipid profile in our study can be attributed to weight loss that has occurred in sitagliptin recipients.

Takihata et el stated that during the study period, there was a statistically significant increase in serum creatinine level in both groups [13]. Hajime Meada et al. studied 1332 T2DM patients. Twenty percent of all these patients were treated with sitagliptin alone, 36% were treated in combination with one other drug, 31% were treated in combination with two other drugs, and 12% were treated in combination with 3 or more drugs. Eventually, they reported that the creatinine level was significantly increased after the intervention [36]. Our results showed that in both groups of patients, creatinine levels increased after

treatment. Although this finding was not statistically significant, it can be attributed to the smaller population and shorter period of treatment. Therefore, it seems that assessment of renal function in patients with these conditions is necessary.

Also, the results from this study showed that sitagliptin in comparison with pioglitazone is slightly better in the reduction of systolic and diastolic blood pressure, but there was no statistically significant difference between two groups in our study regarding systolic and diastolic blood pressure reduction. Mechanisms by which sitagliptin causes a reduction in blood pressure are GLP-1 receptor-mediated endothelial vasodilatation by nitric oxide stimulatory effect, the endothelium-independent vasodilatory effect of GLP-1 and increased excretion of sodium in urine that is done by proximal tubule [37].

Also in this study, there was no significant side effect such as hypoglycemia, oedema of the extremities, gastrointestinal symptoms, liver complications, kidney complications, cardiac complications and eye complications including macular oedema in both combination treatment groups. In Takihata's study, complications such as hypoglycemia (3.4% in the Sitagliptin group and 3.5% in the pioglitazone group) and gastrointestinal complications (5.2% in the Sitagliptin group and 1.8% in the pioglitazone group) were reported [13]. Some of these differences are due to the duration of treatment and antidiabetic drugs that patients were consuming before enrolling in the study. In our study, all patients were treated with metformin, and then sitagliptin or pioglitazone was added to the treatment, but in Takihata's study, patients were treated with metformin, Sulphonylurea or both and then pioglitazone or sitagliptin were added to the treatment. Non-occurrence of hypoglycemia in our study can be attributed to treatment with only metformin. In Chawla's study in line with our study, the patients were treated with metformin, and after enrolling in the study, pioglitazone or sitagliptin was added to their treatment. They did not report any significant side effects [24].

Furthermore in this study, unlike other studies, all patients were selected from those who were treated with only metformin. This kind of selection could help us to modify the effects of previous treatments in patients as a confounding variable.

This study has various limitations. In our study, participants were randomly assigned to treatment groups, but the mean age in two groups was not the same so that metformin-pioglitazone treatment group had higher age than the metformin-sitagliptin group. But in the multivariate model, age was considered as a covariate variable, hence the effects of these two drug regimen were compared by eliminating age. Another limitation of this study was the patients follow up period. Perhaps the time for follow up was not enough for some outcomes such as weight loss. Also, the period of treatment was too short to evaluate long-term glycemic control. On the other hand, in this study, the effects of drugs on insulin resistance was not evaluated. Insulin resistance is an important factor that can determine the outcomes and the rate of response to treatments in T2DM patients.

Finally, it can be concluded that both drug combinations were effective in reducing the levels of HbA1C, fasting blood glucose and blood glucose two hours after a meal and no significant difference was observed between the two treatment groups in improving the outcomes.

It is recommended that further long-term randomised control trials and multi-central studies with larger sample size should be carried out. In this way, we can provide a reference for choosing the best options as dual combination therapy in patients with type 2 diabetes and inadequate glycemic control.

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