VIA MEDICA
ORIGINAL ARTICLE
ISSN 2450–7458
e-ISSN 2450–8187

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Harmful versus beneficial effects of using short-term combined oral antidiabetic therapy: An open-label comparative clinical trial

ABSTRACT

Background. Although oral antidiabetic drugs have many beneficial pleiotropic effects, they are not free from adverse reactions which may interfere with glucose homeostasis. This study aimed to assess the effects of oral antidiabetic drugs as add-on-therapy to metformin, on the metabolic, cardiac and renal determinants.

Material and methods. A total number of seventy-eight type 2 diabetes (T2D) patients who were treated with metformin were allocated to add-on-therapy for 12 weeks, with glimepiride (4 mg/day, n = 26), sitagliptin (100 mg/day, n = 28), and canagliflozin (300 mg/day, n = 24). Anthropometric measurements, glycemic indices, and lipid and renal markers, were determined before and after the treatment.

Results. All of the three treatments significantly decreased the glycemic indices, triglyceride-to-glucose index, and non-significantly altered the serum uric acid-to creatinine ratio. Glimepiride significantly increased the waist-to-height ratio (0.630 ± 0.057 vs. 0.640 ± 0.057, P = 0.040), while sitaglipitin and canagliflozin significantly decreased it (0.650 ± 0.058 versus 0.640 ± 0.054, p = 0.009, and 0.650 ± 0.041 versus 0.630 ± 0.044, P < 0.001). Estimated glomerular filtration rate calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (mL/min/1.73 m^2) significantly declined in patients using glimepiride (109.0 ± 10.4 vs. 103.6 ± 10.9, P = 0.001), and sitagliptin (106.1 ± 12.4 vs. 103.3 ± 15.0, P = 0.013).

Conclusion. Careful selection oral antidiabetic agents can protect T2D patients from harmful events, particularly those related to cardiovascular events and renal function. (Clin Diabetol 2021; 10; 4: 349–353)

Key words: type 2 diabetes, glimepiride, sitagliptin, canagliflozin, waist-to-height ratio, triglyceride-to--glucose index, estimated glomerular filtration rate

Introduction

Several oral antidiabetic drugs related to different categories acting via several mechanisms have been introduced for the management of type 2 diabetes (T2D). Some of them have pleiotropic effects that are either favorable or harmful to the patients. Glimepiride is a long-acting sulfonylurea compound and, like other sulfonylureas, it can cause episodes of hypoglycemia and increase the body weight [1]. It has a beneficial effect on insulin resistance by producing better glycemic control [2]. Several studies highlight a non-harmful effect of glimepiride against cardiac diseases, but it carried also a higher risk of stroke [3]. It has significant unfavorable effects on the renal biomarkers, including cystatin C, serum creatinine, glomerular filtration rate, and urine albumin-to-creatinine ratio [4]. Canagliflozin is a sodium-glucose transporter 2 inhibitor (SGLT-2), which is considered a second-line treatment of T2D [5]. It is a preferred drug in T2D patients with heart failure and/or renal impairment as well as it can be combined with drugs acting on the glucagon like peptide-1 receptor in patients with atherosclerosis [6].

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Clinical Diabetology 2021, 10; 4: 349–353
DOI: 10.5603/DK.a2021.0033
Received: 3.01.2021 Accepted: 8.03.2021

It acts by inhibiting the renal reabsorption of glucose at S1 segment of proximal convoluted tubule, leading to excess excretion of urinary glucose and lowering of blood glucose [7, 8]. Several clinical studies showed its safety in elderly T2D patients with cardiac or renal complications. There is evidence that SGLT-2 inhibitors showed favorable pleiotropic effects on the cardio-renal risk factors, including body weight, glomerular filtration rate (GFR), microalbuminuria, and glycated hemoglobin [9–11]. Sitagliptin is a dipeptidyl peptidase-4 inhibitor that is extensively used in the management of T2D with metabolic derangement or cardio-renal risk factors [12]. In the Sitagliptin Cardiovascular Outcomes Study-Cardiovascular Safety trial, sitagliptin therapy in T2D patients with established cardiovascular disease showed negligible effects on the major adverse cardiac events without increased risk of heart failure [13]. Most previous studies recommended the abovementioned oral antidiabetics with metformin to obtain good glycemic control [14–16]. Moreover, T2D *per se* is a cardio-renal risk factor as well as it is a comorbid disease with cardiac or renal disease. Therefore, this study aimed to compare the effects of oral antidiabetic drugs belonging to different categories as add-on-therapy to metformin on the risk factors related to the metabolic derangement as well as cardiac and renal determinants.

Material and methods

Seventy-eight patients with type 2 diabetes already treated with metformin participated in this open-label clinical trial. The participants were informed about the treatment strategies before they signed the consent form. The ethics committee of the Hawler Medical University approved this study and registered it into the records of the clinical trials (No.276). Eligible patients were of both sexes aged more than 40 years. The criteria of inclusion were T2D patients treated with metformin (median dose 2200 mg daily) for variable periods of time (median duration is 2 years).

Participants who had a history of type 1 diabetes, latent onset type-1 diabetes, systemic disease (including liver, heart, pulmonary, and renal diseases), terminal illness, and those using medicines or herbs that act on the glucose homeostasis during four preceding weeks, pregnancy, nursing mothers, and any history of drug-hypersensitivity reactions were excluded from the study. The sample size was calculated at least 20 patients in this study using α-coefficient (type II error) = 0.05, β-coefficient (type I error) = 0.2, and power = 85%. The patients were randomly allocated for anti-diabetic drugs using a random numbers table.

Group A (26 patients) treated with glimepiride tablet (starting with a small dose and then stepwise increased to achieve glycemic control at 4mg daily, before breakfast.)

Group B (28 patients) treated with sitagliptin tablet (100 mg, before breakfast)

Group C (24 patients) treated with canagliflozin tablet (starting with a small dose and then stepwise increased to achieve glycemic control at 300 mg daily, before breakfast)

Demographic data, a history of metformin therapy, signs and symptoms of unfavorable reactions were recorded. Each patient was fully examined by consultant endocrinologists and the following determinants that related to the objective of the study were measured before initiation of the study and after 12 weeks of treatment with each anti-diabetic drug:

Anthropometric measurements

The weight (kg), height (cm), and waist circumference (cm) were measured. The waist-to-height ratio (WHtR) was simply calculated by dividing the waist (cm) by the height (cm), and a cutoff value of ≥ 0.5 is a predictor of the cardiometabolic risk factor [17].

Measurements of glycemic indices, lipid profile and renal indices:

Fasting plasma glucose (FPG), glycated hemoglobin (HbA_{1c} %), fasting serum triglyceride, serum uric acid and creatinine were determined in the Laboratories of Layla Qassim Diabetic Center as routine investigations. The following determinants were calculated:

Triglyceride-to-glucose index (TYG) =

$$\text{LN}\ \frac{\text{fasting serum triglyceride (mg/dL)} \times \text{fasting plasma glucose (mg/dL)}}{2}\ [18]$$

Serum uric acid-to creatinine ratio (UA/Cr ratio)

Estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) formula [19]:

$eGFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times \times 0.993^{Age} \times 1.018$ [if female] *minus* 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Statistical analysis

The results are expressed as a number, median, and mean ± SD. The data were analyzed using an independent two-sample two-tailed paired Student's t-test, and Spearman's correlation test, taking a P-value of ≤ 0.05 as the lowest limit of significance. Excel 2010 software was applied for the statistical analysis.

Table 1. Baseline data

Variables	Group A Glimepride (n = 26)	Group B Sitagliptin (n = 28)	Group C Canagliflozin (n = 24)
Age (year)	48.0	48.5	46.5
Sex (Male: Female)	10:16	7:21	11:13
Duration of diabetes (year)	3.25	4	4
Metformin dosage (mg)	2,200	2.200	2,350
Duration of metformin therapy (year)	2.0	2.0	2.25

The results are expressed as median value

Results

A total of seventy-eight patients allocated to three treatment groups completed twelve weeks of treatment with regular follow-up. The baseline characteristics of the participants are shown in Table 1. It was observed that in all three groups the age, duration of T2D, and using metformin therapy were insignificantly different. Regarding the sex ratio (male-to-female), Group B showed a lower ratio compared with Group A and C.

Table 2 showed that TYG significantly correlated with FPG ($r = 0.572$, $P < 0.001$), and WHtR ($r = 0.304$, $P = 0.007$). eGFR significantly correlated with UA/Cr ratio ($r = 0.342$, $P = 0.002$) and inversely with WHtR (–0.272, $P = 0.016$). In the groups treated with sitagliptin or canagliflozin, there was a significant reduction of FPG and WHtR after 12 weeks of treatment compared to the corresponding baseline data (Table 3). Canagliflozin reduced the FPG by 36.2%, while glimepiride and sitagliptin reduced the FPG by 29.7% and 25%, respectively. Glimepiride increased the WHtR by 1.6% while sitagliptin and canagliflozin reduced the WHtR by 1.6% and 3.1%, respectively. A significant reduction of eGFR was observed in patients treated with glimepiride and sitagliptin, which accounted for 5.3% and 2.6%, respectively. Canagliflozin significantly improved the eGFR by 0.5% increment. Table 3 shows that the reduction of eGFR was significant in Groups A and B. None of the three treatments significantly decreased serum UA/Cr ratio. Episodes of hypoglycemia were not reported in any treatment group.

Table 2. Baseline correlations between fasting serum glucose and metabolic and renal indices

	TYG	UA/Cr ratio	eGFR	WHtR
FPG	0.572	–0.184	0.080	0.058
	P < 0.001	P = 0.107	P = 0.487	P = 0.614
TYG		–0.097	–0.040	0.304
		P = 0.398	P = 0.725	P = 0.007
Serum UA/			0.342	–0.067
/Cr ratio			P = 0.002	P = 0.560
eGFR				–0.272
				P = 0.016

The results are presented as Spearman's correlation coefficient. P: probability, FPG: Fasting plasma glucose, TYG: Triglyceride-glucose index. UA/Cr ratio: Serum uric acid-to creatinine ratio, eGFR: Estimated glomerular filtration rate calculated using CKD-EPI formula, WHtR: waist-to height ratio

Discussion

In this study, a significant correlation between the glycemic index and renal indices with the cardiometabolic risk factors represented by WHtR and TYG in T2D were observed. In all the three treatments, the cardiometabolic risk factors were improved to a certain extent while the eGFR was declined in Group A (treatment with glimepiride) and Group B (treatment with sitagliptin). This study agreed with previous studies that show T2D patients have multi-cardiometabolic risk factors, including obesity and dyslipidemia. Browning et al. reported that WHtR = 0.5 is a predictor of diabetes and cardiovascular events in both sexes of the population, which indicates that the study patients are at risk of developing cardiovascular events [20]. Therefore, glimepiride therapy can contribute to the development of cardiovascular events in T2D, because it increases significantly the WHtR by 1.6% over 12-week treatment [21]. Sitagliptin and canagliflozin improved one of the risk factors of cardiovascular diseases, which is a significant decrease in WHtR [22]. Triglyceride-to-glucose index was significantly decreased by using glimepiride, sitagliptin, and canagliflozin, but canagliflozin more effectively reduced the TYG compared with glimepiride, or sitagliptin (8.2% vs. 3.9% and 4.5%). This finding agreed with the previous study that showed long term therapy of canagliflozin over 52 weeks was highly effective against the components of metabolic syndrome compared with glimepiride and sitagliptin [23]. None of the three treatments had a significant effect on the serum UA/Cr ratio. A recent study demonstrated that sitagliptin increased the serum uric acid level that was significantly correlated with HOMA-B, which indicates

Table 3. Effect oral antidiabetic drugs on metabolic and renal indices

Variables	Glimepiride (n = 26)			Sitagliptin (n = 28)			Canagliflozin (n = 24)		
	Before	After	P-value	Before	After	P-value	Before	After	P-value
Weight (kg)	79.6 ± 13.8	81.5 ± 13.2	< 0.001	89.1 ± 17.1	88.0 ± 16.7	0.001	83.9 ± 15.2	81.1 ± 15.2	< 0.001
Height (m)	1.62 ± 0.09	1.62 ± 0.09	1.000	1.6 ± 0.09	1.6 ± 0.09	1.000	1.6 ± 0.07	1.6 ± 0.07	1.000
Waist circumference (cm)	102.1 ± 7.5	103.9 ± 8.9	0.032	104.1 ± 7.3	101.6 ± 6.9	0.008	104.0 ± 6.4	100.6 ± 6.6	< 0.001
Body mass index (kg/m^2)	30.4 ± 4.7	31.1 ± 4.6	< 0.001	34.7 ± 6.3	34.3 ± 6.0	< 0.001	32.7 ± 5.4	31.6 ± 5.4	< 0.001
Waist-to-height ratio	0.630 ± 0.057	0.640 ± 0.059	0.040	0.650 ± 0.058	0.640 ± 0.054	0.009	0.65 ± 0.044	0.63 ± 0.044	< 0.001
Fasting plasma glucose (mg/dL)	235.4 ± 90.2	165.5 ± 63.4	0.001	211.2 ± 82.0	158.3 ± 49.1	< 0.001	229.1 ± 64.3	146.2 ± 48.2	< 0.001
Glycated hemoglobin (%)	9.1 ± 1.3	7.2 ± 1.0	< 0.001	9.2 ± 1.1	7.8 ± 1.2	< 0.001	9.4 ± 1.1	7.1 ± 0.9	< 0.001
Fasting serum triglyceride (mg/dL)	198.5 ± 105.7	182.8 ± 86.5	0.314	210.9 ± 108.8	169.8 ± 71.7	0.005	200.5 ± 88.1	141.1 ± 67.5	0.012
Serum uric acid(mg/dL)	4.1 ± 0.9	4.7 ± 1.0	< 0.001	4.1 ± 0.9	4.2 ± 0.9	0.548	4.1 ± 0.7	3.9 ± 0.7	0.104
Serum creatinine (mg/dL)	0.65 ± 0.1	0.71 ± 0.1	< 0.001	0.66 ± 0.1	0.69 ± 0.1	0.004	0.69 ± 0.1	0.70 ± 0.1	0.207
Triglyceride-glucose index	9.84 ± 0.69	9.46 ± 0.61	0.008	9.82 ± 0.69	9.38 ± 0.54	< 0.001	9.91 ± 0.53	9.10 ± 0.59	< 0.001
Serum uric acid-to-serum creatinine ratio	6.43 ± 1.78	6.43 ± 1.78	1.000	6.34 ± 1.65	6.14 ± 1.63	0.262	6.06 ± 1.04	5.62 ± 1.11	0.052
Estimated glomerular filtration rate-epidemiology collaboration	109.4 ± 10.4	103.6 ± 10.9	0.001	106.1 ± 12.4	103.3 ± 15.0	0.013	107.5 ± 7.0	107.0 ± 7.6	0.576

The results are expressed as mean ± SD. P-value was calculated by independent two-sample paired t-test (two-tailed)

a link between pancreatic beta-cell function and antihyperglycemic efficacy [24]. Other studies report that canagliflozin had dual effects on the serum levels of uric acid and this effect depended on the baseline serum uric acid level [25]. Canagliflozin improves the serum uric acid if the baseline value is low and vice versa [25, 26]. Therefore, the effect of antidiabetic agents on the serum uric acid is variable, despite the fact that there is a link between serum uric acid level and the function of the pancreatic beta-cell. Both glimepiride and sitagliptin adversely reduced the renal function, which was reflected by the evidence of decreasing the eGFR values. This observation agreed with previous work that reported sitagliptin can reduce the renal function in T2D, but this effect was not associated with cardiovascular outcome events [27]. Previous studies showed that glimepiride can impair renal function, while long term therapy with canagliflozin slowly reduced the renal function, which is dose-independent [28]. Thus, slow decline of the kidney function during canagliflozin therapy suggests that canagliflozin offered cardiorenal protection [29]. Short-term canagliflozin therapy that was applied in this study does not show the harmful effect of canagliflozin on the renal function, which is in agreement with a study by Takashima et al. who reported a decline of eGFR by 0.7 mL/min/1.73 m^2 in T2D patients treated with canagliflozin for 52 weeks. In brief, anti-diabetic agents have multiple pharmacological actions beyond their effect on glucose homeostasis. Canagliflozin has a favorable effect on the cardiometabolic and renal protection indices, while glimepiride has harmful effects on cardiovascular risk factors and renal function. The strength of the study is using three medications related to three different mechanisms of action and using short-term therapy, which eliminates the confounding factors that occur with long term therapy. The most important limitation of the study is the small sample size.

We conclude that oral antidiabetics are not free from adverse reactions that participate in increasing the burden of cardiovascular events and renal impairment. Careful selection of oral antidiabetic agents can protect T2D patients from harmful events.

Acknowledgement

The authors thank the Dean of the College of Pharmacy for his kindly support to achieve this work.

Conflict of interest

The authors report no conflicts of interest

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