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RESEARCH ARTICLE

Efficacy and Safety of Canagliflozin Compared to Sitagliptin and Glimepride as Add- on Therapy in T2DM

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Abstract

Diabetes type II is a progressive disease and associated with many complications. Metformin is the first-line pharmacological therapy for type II. However, there is a second anti-diabetic drug can be added for patients who do not achieve sufficient glycemic control with metformin. In this study, we assess the efficacy and safety of newly approved anti-diabetic drugs Canagliflozin compared to Sitagliptin and Glimepiride patient with type II diabetes. Basically, 210 diabetic patients have received Canagliflozin 300 mg or Sitagliptin 100 mg or Glimepiride 4 mg for at least 16 weeks. Previously, the patient's glycemic state was uncontrolled by Metformin monotherapy. Glycated hemoglobin and Fasting blood glucose changes were used as an efficacy assessment from the baseline after metformin discontinuation. The safety profile was determined by comparing patient's lipid profile, renal function, BUN, renal function and uric acid. Our results had shown a significant reduction in HBA1c and FBS in the three groups after 4 months of treatment ($p < 0.05$). However, there was no significant change in the reducing effect between the three drugs ($p = 0.704, 0.521$). Canagliflozin and Glimepiride produce more reduction in triglycerides than Sitagliptin through the treatment period, although it is not significant, the change in the effect was significantly higher in Canagliflozin and Glimepiride comparing to Sitagliptin. Unlike Canagliflozin, Glimepiride and Sitagliptin produce a significant reduction in LDL after 4 months of treatment ($p = 0.0318, 0.047$) and significant difference in the effect ($p = 0.042$). Canagliflozin cause a significant elevation in LDL after the initiation of therapy ($p = 0.034$). The effect of Canagliflozin was significantly higher on HDL comparing to Glimepiride and Sitagliptin throughout the treatment ($p = 0.048$) and as a difference in the effect ($p = 0.043$). Canagliflozin and Glimepiride produce a significant elevation in BUN comparing to Sitagliptin ($p = 0.004, 003$), whereas, Canagliflozin and Sitagliptin produce a higher reduction in GFR than Glimepiride. Glimepiride is significantly elevates serum uric acid comparing to Canagliflozin and Sitagliptin with $p = 0.0406$. Conclusion: Canagliflozin, Sitagliptin, and Glimepiride are effective add-on therapy with metformin for proper control of blood glucose in T2DM. Canagliflozin and Glimepiride improve TGs and LDL greater than Sitagliptin. Sitagliptin produces less elevation in BUN than Canagliflozin and Glimepiride. Canagliflozin and Sitagliptin required renal monitoring throughout treatment.

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease and patients often required combinations of anti-hypoglycemic drugs to maintain glycemic control. Metformin is the recommended first-line therapy for T2DM. A second anti-hyperglycemic drug is usually added for a patient that does not achieve sufficient glycemic control with metformin [1, 2].Dipeptidyl peptidase-4 inhibitors or Gliptins are another class of anti-hyperglycemic drugs is commonly used as a second additive drug widely used. Gliptins inhibit DPP-4, which degrades incretins from the intestine; therefore, Incretins are increased and control postprandial glucose

blood level [3, 4]. T2DM has well recognized as an independent risk factor for cardiovascular disease that predisposing to diabetic cardiomyopathy and atherosclerotic cardiovascular disease (CVD), which could lead to heart failure through a variety of mechanisms, including myocardial infarction and chronic pressure overload [5].

Treatment of risk factors, such as diabetes, is very important in reducing the risk of cardiovascular diseases [6].In addition to improved glucose control; novel treatment would ideally provide a reduction of cardiovascular risk, with a favorable effect on excess weight, and low intrinsic hypoglycemic risk as well as a synergistic mechanism of action for broad combination therapy.

With the development of sodium-glucose co-transporter 2 (SGLT2) inhibitors, an anti-diabetic pharmacologic option has recently become available that comes close to meeting these requirements [7].Sodium-glucose cotransporter-2 (SGLT2) inhibitors, including empagliflozin, dapagliflozin, and canagliflozin, are now widely approved antihyperglycemic therapies. Because of their unique glycosuric mechanism, SGLT2 inhibitors can play role in weight reduction as well. Furthermore, the osmotic diuretic and natriuretic effects contributing to plasma volume contraction, and decreases in systolic and diastolic blood pressures by 4 to 6 and 1 to 2 mm Hg, respectively, which may underlie cardiovascular and kidney benefits [8].

Obesity/overweight is a risk factor for cardiovascular disease and T2DM, among other diseases. Most patients with T2DM are obese/ overweight. Thus, obesity and T2DM may have mutual treatment. Canagliflozin, the first sodium-glucose co-transporter (SGLT) 2 inhibitor, has been approved by the US FDA to treat T2DM. Interestingly, a recent study has revealed weight loss after administration of canagliflozin in the early treatment of diabetes [9].

Current guidelines for the treatment of T2DM indicate a patient-centered approach that should go beyond glycemic control. Of the many anti-hyperglycemic agents available for treatment of T2DM, sodium-glucose co-transporter 2 (SGLT2) inhibitors offer the advantages of reduced glycated hemoglobin (A1C), body weight (BW), and systolic blood pressure (SBP) and are associated with a low risk of hypoglycemia when used either as monotherapy or with other agents not typically associated with increased risk of hypoglycemia [10]. Additionally, Canagliflozin has been shown to have beneficial effects on high-density lipoprotein cholesterol (HDL-C) and triglyceride levels, likely as a result of improvements in glycaemic control and reductions in body weight [11].

The Common side effects of SGLT-2 inhibitors include genital yeast infections, urinary tract infections, and hypotension. However, in May 2015, the Food and Drug Administration (FDA) issued a drug safety communication, which reported that these medications might lead to diabetic ketoacidosis (DKA) [12].This study was aimed to evaluate the efficacy and safety of Canagliflozin versus Sitagliptin and Glimepiride as add on therapy to metformin in type 2 diabetic patients.

Material and Methods

A total of 210 patients participate in this randomized clinical study, which is carried out in Princess Basma Teaching Hospital/ Jordan and Medical City/Iraq through January 2019 to August 2019. The patients are categorized into three groups. Group A: patients taking metformin plus Canagliflozin 300 mg/day, group B: patients taking metformin plus Sitagliptin 100 mg/ day, and Group C: patients taking metformin plus Glimepiride 4mg/ day. Approval was obtained from the ethical committee of Philadelphia University/Jordan.

All participants provided verbal information consent for participation. The included criteria were patients aged 20-65 years with T2DM inadequately controlled by metformin 1500 mg/day (HbA1c ≥ 7.0%) for more than 4 months and eGFR ≥ 60-ml/min/1.73 m3 at the time of involvement. The excluded criteria were patients with a history of diabetic ketoacidosis, cardiovascular disease, renal or hepatic disease, uncontrolled hypertension, type 1 diabetes, patients using insulin or any other than metformin as ant hyperglycemic drugs and pregnant women.

Measurements

All patients were instructed to adhere to specific dilatory and medical strategies and record any additional medication could be used throughout the study period that may

interfere with the results. Basal value and 16 weeks from the beginning of the treatment, for all patients HbA1c, Fasting blood glucose, TGs, LDL, Cholesterol, HDL, BUN, Creatinin, and Uric acid were evaluated using commercial kits usually used by the hospital lab.

Statistical Analysis

Study groups were compared with respect to all variables; the mean value was expressed as the mean ± standard deviation (SD). Using paired t-test to analyze the significance of the difference in the mean of two paired samples and Chi-square test compared categorical variables. For continuous variables, one-way ANOVA test was used to evaluate the significant differences. P-value < 0.05 was considered as statistically significant. For statistical analysis, IBM SPSS version 22 was used.

Results

Table 1 illustrates the demographic and specific disease characteristics distribution of the patients and was not significantly varied between the studied groups (p >0.05).

Table 1: the demographic distribution of the patients

Group		Canagliflozin	Sitagliptin	Glimepride	P value
Male		42	49	27	0.57
Female		32	31	29	0.94
Total No.		74	80	56	
Age Mean ± SD		48.43 ± 7.35	44.28 ± 6.82	43.94 ± 8.14	0.74
BMI (Kg/m²)		38.94±4.96	36.24±7.15	37.42±4.56	0.094
Body Wt. (Kg)		81.45±17.45	84.03±14.76	79.64±18.20	0.195
Smoker (%)		10 (13.51%)	12 (15%)	7 (12.5%)	0.079
Blood pressure mmHg	Diastolic	86.34±8.21	88.34±5.15	84.95±6.24	0.845
	Systolic	127.85±6.82	131.85±8.63	134.48±8.65	0.084
HbA1c%		9.8±1.45	9.6±1.73	9.9±1.69	0.78
eGFR ml/min/1.73 m³		104.65±22.56	98.53±26.95	112.52±29.22	0.098

There was a significant reduction in HBA1c and FBS in the three groups after 4 months of treatment (p <0.05), but there is no significant change in the reducing effect of between the three drugs (p >0.05) (Table 2, 3 and Figure 1, 2).Canagliflozin and Glimepiride produce more reduction in triglycerides than Sitagliptin through the treatment period, although it is not significant (p >0.05), the mean difference in their effect was significantly larger than Sitagliptin (p = 0.0486) (Table 4 and Figure 3). Unlike Canagliflozin Glimepiride and Sitagliptin produce a significant reduction in LDL after 4 months of treatment (p = 0.0318, 0.047) and Sitagliptin was more powerful. The change in LDL was significant between the three drugs (p= significant difference in the effect (p = 0.042) (Table 5 and Figure 4). Canagliflozin result in a significant elevation in LDL after 4 months of treatment (p=0.034). The reducing effect of Canagliflozin was significantly greater on HDL than Glimepiride and Sitagliptin throughout treatment (p = 0.048) and as a difference in the effect (p =0.043) (Table 6 and Figure 5).Canagliflozin and Glimepiride produce a significant elevation in BUN comparing to Sitagliptin (p = 0. 004, 003) (Table 7 and Figure 6), whereas, Canagliflozin and Sitagliptin produce a higher reduction in GFR than Glimepiride (p = 0. 007, 0.38, 0.246) (Table 8 and Figure 7).Glimepiride in significantly elevates serum uric acid comparing to Canagliflozin and Sitagliptin with p vale 0.047 (Table 9 and Figure 8).

Table 2: Effects of Canagliflozin, Sitagliptin and Glimepride on HBA1c

Drug	HbA1c (%)		P value (paired T-test)	Mean difference	P-value (one-way ANOVA
	Pre-treatment	Post-treatment (4 months)			
Canagliflozin	9.8 ± 1.45	7.68 ± 1.23	.000	-2.12 ± 1.11	.704
Sitagliptin	9.6 ± 1.73	7.58 ± 1.54	.000	-2.02 ± 0.85	
Glimepride	9.9 ± 1.69	7.76 ± 1.31	.000	-2.14 ± 1.04	

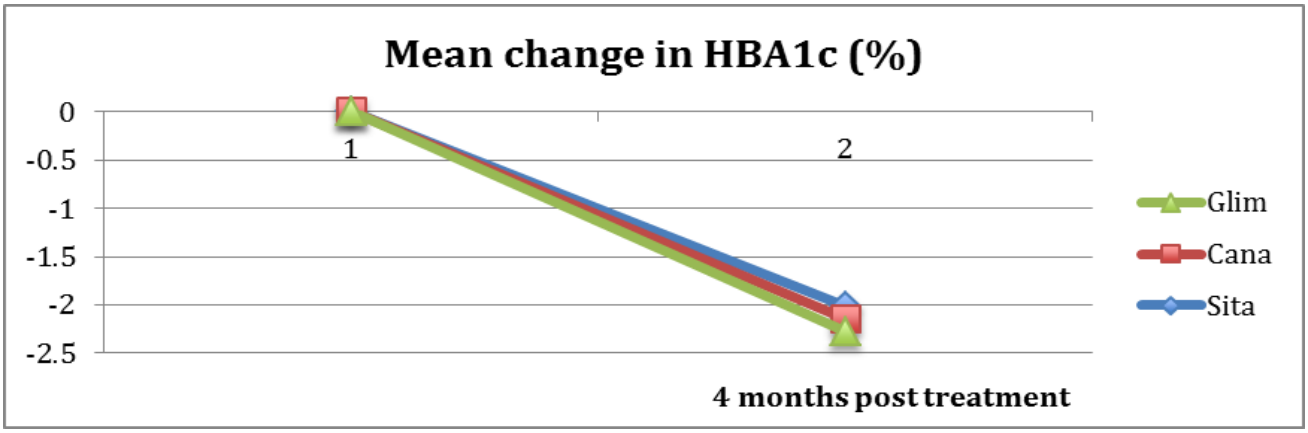

Figure 1: Effects of Canagliflozin, Sitagliptin and Glimepride on HBA1c

Table 3: Effects of Canagliflozin, Sitagliptin and Glimepride on Fasting blood glucose

Drug	Fasting blood glucose (mg/dl)		P value (paired T-test)	Mean difference	P-value (one-way ANOVA
	Pre-treatment	Post-treatment (4 months)			
Canagliflozin	214.43±49.54	152.45±42.34	.002	-61.98 ± 42.13	.521
Sitagliptin	223.28±62.01	163.62±46.27	.003	-59.66 ± 62.45	
Glimepride	229.54±79.23	172.87±58.92	.001	-56.67 ± 77.18	

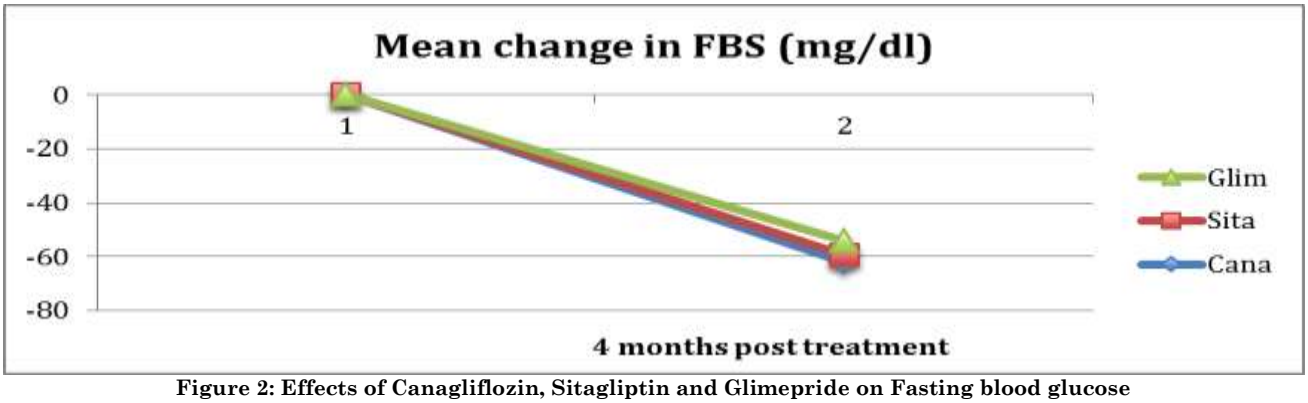

Figure 2: Effects of Canagliflozin, Sitagliptin and Glimepride on Fasting blood glucose

Table 4: Effects of Canagliflozin, Sitagliptin and Glimepride on TGs

Drug	TGs (mg/dl)		P value (paired T-test)	Mean difference	P-value (one-way ANOVA
	Pre-treatment	Post-treatment (4 months)			
Canagliflozin	186.45 ± 68.41	175.27 ± 48.32	.0548	-11.18 ± 23.72	.0486
Sitagliptin	192.30 ± 95.34	186.36 ± 38.52	.748	-5.94 ± 26.92	
Glimepride	203.65 ± 73.93	192.41 ± 51.83	.0594	-11.24 ± 47.76	

Post-hoc test: Cana and Glim with Sitag.

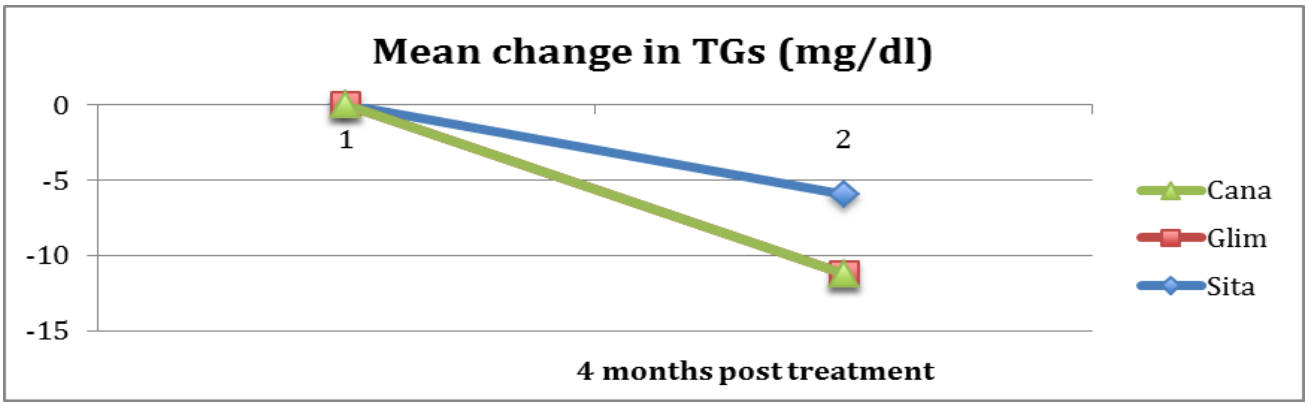

Figure 3 Effects of Canagliflozin, Sitagliptin and Glimepride on TGs

Table 5: Effects of Canagliflozin, Sitagliptin and Glimepride on LDL

Drug	LDL (mg/dl)		P value (paired T-test)	Mean difference	P-value (one-way ANOVA
	Pre-treatment	Post-treatment (4 months)			
Canagliflozin	136.44 ± 37.42	142.58 ± 35.43	0.034	6.14	0.042
Sitagliptin	128.89 ± 42.43	122.32 ± 38.12	0.0318	-6.57	
Glimepride	131.43 ± 31.42	128.40 ± 32.48	0.047	-3.03	

Post-hoc test: Cana and Glim with Sitag.

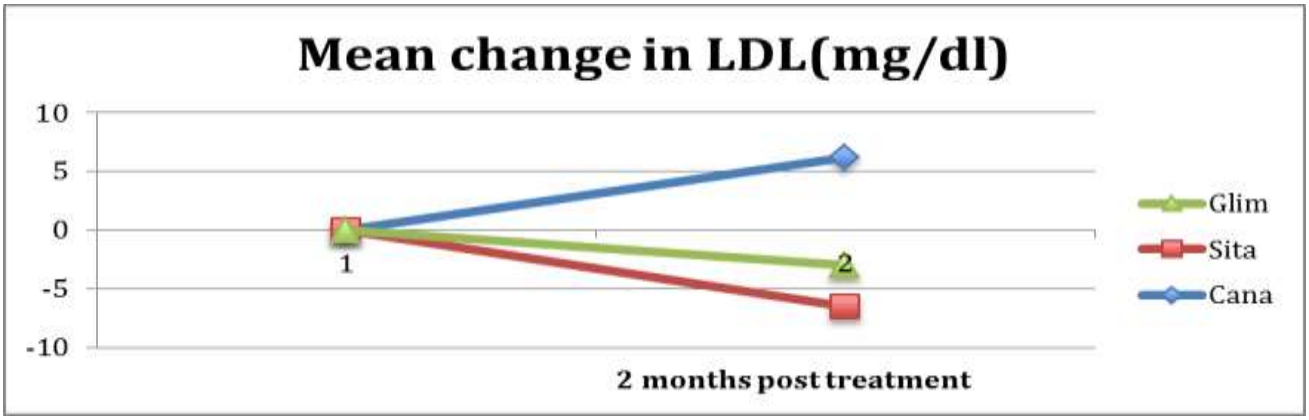

Figure 4: Effects of Canagliflozin, Sitagliptin and Glimepride on LDL

Table 6: Effects of Canagliflozin, Sitagliptin and Glimepride on HDL

Drug	HDL		P value (paired T-test)	Mean difference	P-value (one-way ANOVA
	Pre-treatment	Post-treatment (4 months)			
Canagliflozin	41.43 ± 6.34	44.57 ± 7.51	0.048	-3.14 ±2.32	0.043
Sitagliptin	44.19 ± 8.54	46.53 ± 9.54	0.784	-2.34 ± 1.54	
Glimepride	39.94 ± 11.52	42.52 ± 12.72	0.089	-2.58 ±1.96	

Post-hoc test: Sitag and Glim with Cana.

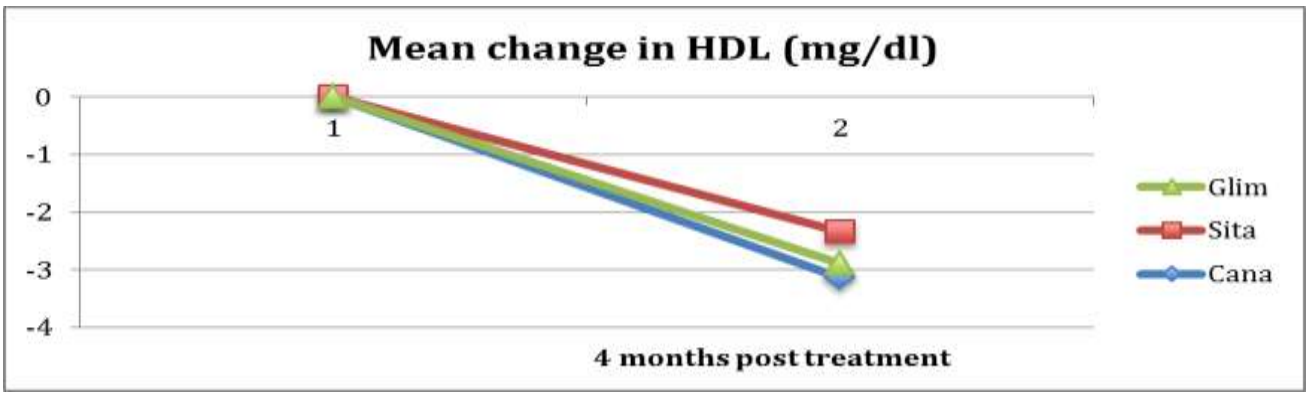

Figure 5: Effects of Canagliflozin, Sitagliptin and Glimepride on HDL

Table 7: Effects of Canagliflozin, Sitagliptin and Glimepride on BUN

Drug	Blood Urea Nitrogen (mg/dl)		P value (paired T-test)	Mean difference	P-value (one-way ANOVA
	Pre-treatment	Post-treatment (4 months)			
Canagliflozin	19.55 ± 6.43	21.32 ± 7.54	.004	-1.77	0.039
Sitagliptin	20.53 ± 4.60	21.52 ± 4.77	.326	-0.99	
Glimepride	20.92 ± 5.61	24.51 ± 8.64	.003	-3.59	

Post-hoc test: Cana and Glim with Sitag.

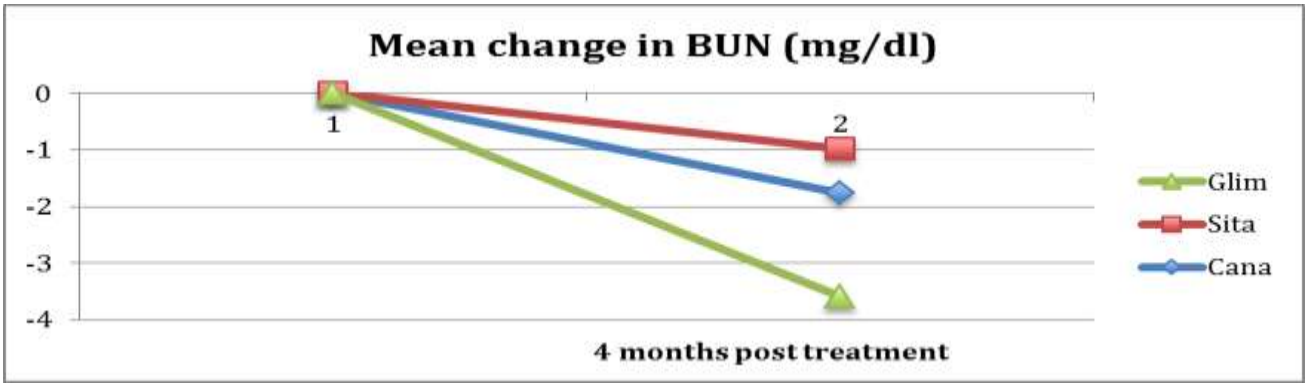

Figure 6 Effects of Canagliflozin, Sitagliptin and Glimepride on BUN

Table 8: Effects of Canagliflozin, Sitagliptin and Glimepride on eGFR

Drug	eGFR (ml/min/1.73 m²)		P value (paired T-test)	Mean difference	P-value (one-way ANOVA
	Pre-treatment	Post-treatment (4 months)			
Canagliflozin	106.39 ± 32.02	101.42 ± 18.17	.007	4.97 ± 8.32	.046
Sitagliptin	103.22 ± 44.31	98.56 ± 37.41	.038	4.66 ± 9.71	
Glimepride	97.43 ± 34.51	95.62 ± 33.61	.246	1.81 ± 4.62	

Post-hoc test: Cana and Sitag with Glim.

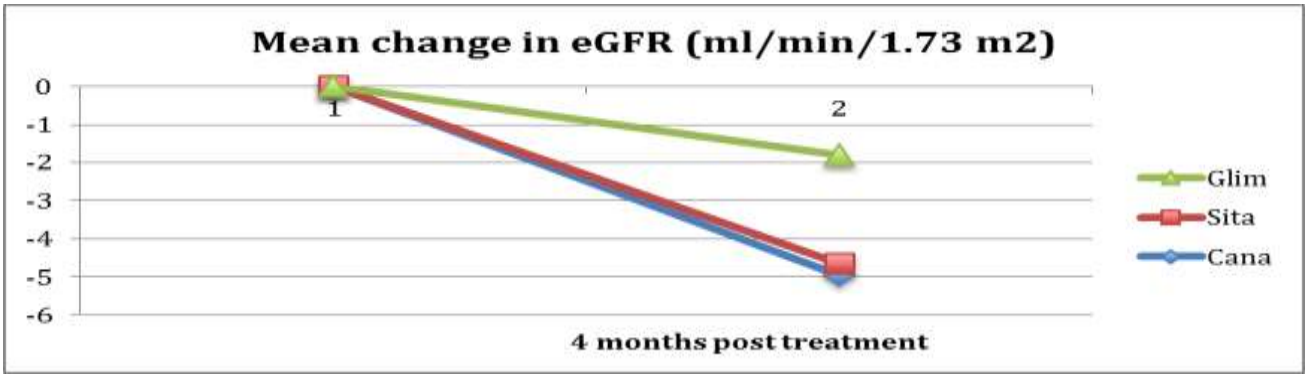

Figure 7: Effects of Canagliflozin, Sitagliptin and Glimepride on eGFR

Table 9: Effects of Canagliflozin, Sitagliptin and Glimepride on Uric acid

Drug	Uric acid (mg/dl)		P value (paired T-test)	Mean difference	P-value (one-way ANOVA
	Pre-treatment	Post-treatment (4 months)			
Canagliflozin	4.93 ± 1.42	5.46 ± 1.83	.058	-0.53	.0406
Sitagliptin	4.26 ± 1.26	4.93 ± 1.64	.047	-0.67	
Glimepride	6.08 ± 1.02	6.12 ± 1.04	.246	-0.04	

Post-hoc test: Cana and Glim with Sitag.

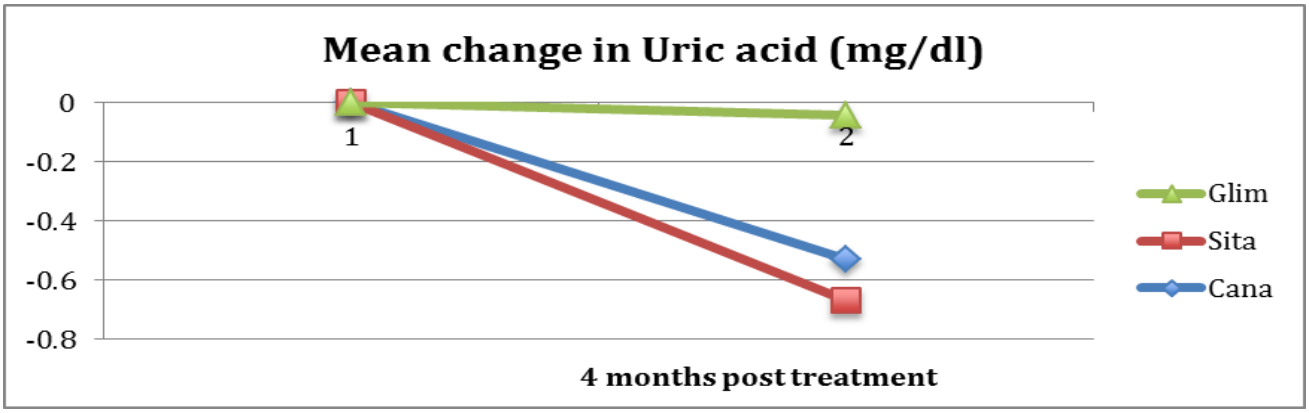

Figure 8: Effects of Canagliflozin, Sitagliptin and Glimepride on Uric acid

Discussion

Patient with T2DM often required additional anti-diabetic drugs to control blood glucose with metformin in case of progression of the disease. The availability of many additive anti-diabetic drugs that have has a distinct risk/benefit effect make the importance of appropriate selection [13]. The main outcomes of treating T2DM are the achievement of glucose reduction with low risk of hypoglycemia concurrent with the reduction in cardiovascular risk factors and control body weight [14]. This study was focused on the comparison of two commonly used anti-diabetic drugs, Sitagliptin and Glimepiride, with Canagliflozin.

The comparison was applyed by selecting patients with T2DM inadequately controlled by metformin. The addition of Canagliflozin 300 mg daily for 4-month resulted in significant improvement in HBA1c and FBS. This is in agreement with Juan et al (2016), who found Canagliflozin in both 100 mg twice daily and 300 mg once daily produces a significant reduction in HBA1c and FBS comparing to the control patients [15]. For Sitagliptin, Maryam et al (2017) showed that 12 weeks addition of Sitagliptin 100 mg daily to metformin resulting in a significant reduction in HBA1c and FBS [16] this is consistent with our result as Sitagliptin 100 mg for 4 months significantly reduced both HBA1c and FBS. The use of Glimepiride 4 mg in combination with metformin in this study resulted in significant reduction in both HBA1c and FBS, this results are consistent with Kabadi UM and Kabadi M (2006) who found addition of Glimepiride in patients with T2DM who are inadequately controlled by metformin alone result in significant reduction of HBA1c and FBS [17].

In this work, the effect of adding Canagliflozin 300 mg, Sitagliptin 100 mg, and Glimepiride 4 mg, although all of them significantly lower HBA1c and FBS, Canagliflozin was superior to Sitagliptin. This results support the finding from Thomas et al (2017) who found a more beneficial

effect from Canagliflozin on HBA1c and FBS in comparison to Sitagliptin [18].

A 52-week randomized trial suggests that Canagliflozin may be a new therapeutic tool providing better improvement in glycemic control than Sitagliptin [19]. Our finding shows the greater lowering effect of Glimepiride on HBA1c than Canagliflozin and Sitagliptin. This is not consistent with many studies, which support the superior effect of Canagliflozin between the other [20, 21]. This could be due to the relatively short period of treatment or the poor patient complying with the researcher's advice, this is supported in our results that show a superior effect of Canagliflozin to Glimepiride on FBS. Regarding the efficacy of these three drugs, in this study we found a non-significant difference between these drugs on the final outcome by comparing the mean of reduction in both HBA1c and FBS.

A close link exists between DM and cardiovascular disease (CVD), which is the most prevalent cause of morbidity and mortality in diabetic patients. Cardiovascular (CV) risk factors such as obesity, hypertension, and dyslipidemia are common in patients with DM, placing them at increased risk for cardiac events [22]. Diabetes mellitus is associated with a considerably increased risk of premature atherosclerotic cardiovascular disease. Dyslipidemia is common in diabetes and there is strong evidence that cholesterol lowering improves cardiovascular outcomes [23].

In this study, Canagliflozin and Glimepiride were significantly improved fasting TGs, while Sitagliptin affects LDL more than TGs. Cusi K et al (2018) a double-blind, parallel-group, placebo-controlled, 24-week trial concluded that Canagliflozin decreases TGs by 6.9%and strongly associated with weight loss [24]. Other studies confirm the lowering effect of Glimepiride on TGs [25].

Sitagliptin alone or in combination resulted in a more favorable lipid profile. A retrospective study indicated that administration of Sitagliptin significantly improved serum levels of TG, TC, and LDL-C except for serum HDL-C levels in patients with T2DM during 90 to 365 days follow-up period [26]. In respect to LDL, many studies observed an increase in the LDL is associated with the use of Canagliflozin. Boyu et al (2018) showed that 26 weeks treatment of Canagliflozin 100 mg and 300 mg both increase LDL-c from baseline compared with the control patients [27]. The mechanism of this effect is the reduced clearance of LDL from the circulation and greater lipolysis of triglyceride-rich lipoproteins [28].

In this work, we observed a significant increment of LDL 4 months after Canagliflozin therapy. In contrast, Sitagliptin and Glimepiride cause a reduction in LDL in patients post-treatment comparing to pretreatment. Regarding HDL, this study found increased HDL level by Canagliflozin and Glimepiride more than Sitagliptin. These effects are generally known to contribute to a reduced risk of cardiovascular events [29]. There were favorable effects of Canagliflozin compared with placebo HDL seen by many studies [30, 31]. Araki et al (2009) confirm the effect of Glimepiride on HDL-c level.

The mechanism of this effect is by improving plasma adiponectin level especially in a patient with T2DM comparing to a high level of adiponectin before treatment [32].Sitagliptin has been reported to improve lipid profiles, but findings from these studies are conflicting. In randomized clinical trials that investigated the effect of Sitagliptin on lipid profiles revealed that Sitagliptin alone achieved greater improvement in serum TG, TC, and HDL-C levels [33].

On the other hand, Long-term treatment with the Sitagliptin appeared to be associated with a greater reduction in serum HDL levels [34]. Shigematsu et al (2014) reported that sitagliptin significantly reduced serum TC, LDL-C, and non-HDL-C, particularly in patients with high baseline TG concentrations after 12 weeks' treatment [29]. In this study, Sitagliptin elevates HDL but not significantly; this could be illustrated more precisely by longer-term therapy. Specific endpoints of interest in this study were included changes in blood urea nitrogen (BUN), eGFR, and uric acid.

(BUN) was significantly elevated with Canagliflozin and Glimepiride. In contrast, Sitagliptin does not cause an elevation in BUN. Canagliflozin demonstrated a higher elevation in BUN in comparison to Sitagliptin in randomized, double-blind, placebo- and active-controlled subjects, this study compares Canagliflozin 100 mg daily and Canagliflozin300 mg daily with

Sitagliptin 100 mg daily. The change from baseline of BUN was seen larger by a high dose of Canagliflozin. The osmotic diuretic effect of high glucose excretion from the kidney may be the cause of high BUN with Canagliflozin [35]. In another study, the chronic sitagliptin administration was able to decrease BNU to levels analogous to those observed in lean controls, suggesting amelioration of kidney function [36].

Elevation of BUN with was Glimepiride confirmed by Leiter et al (2015) who found an average elevation in BUN was 5.8 and compared Glimepiride with Canagliflozin which result in greater elevation with Canagliflozin [37].Assessment of renal function is applied clinically by a number of clinical laboratory tests. The most practical test is to estimate the glomerular filtration rate (eGFR) [38]. Canagliflozin is not approved for treating T2DM in peoples with eGFR less 45ml/min/1.73 m2 because the efficacy of Canagliflozin is dependent on renal function [39].

There are many studies carried to determine the effect of Canagliflozin on renal function. A randomized controlled study of 2 years of follow-up data comparing Canagliflozin to Glimepiride showed that Canagliflozin produces a progression of renal function decline in patients with T2DM [40]. The incidence of renal adverse effect was studied in patients with T2DM who randomized to receive Canagliflozin, Sitagliptin or Glimepiride; the results of renal adverse effect were similar for the three drugs used, with the incidence of adverse effect consistent with Canagliflozin over 2 years.

The renal related adverse effect was occurred early with Canagliflozin compared with Glimepiride [41]. The United States Food and Drug Administration (FDA) warned of the risk of acute kidney injury for canagliflozin and dapagliflozin, probably reflect the acute initial changes in eGFR as a result of renal hemodynamic effects with canagliflozin and other SGLT2 inhibitors [42].

Sitagliptin use also results in mean eGFR reduction, which was confirmed by many studies. Jan et al. (2016) showed the mean eGFR reduction over 4 years from baseline was greater in the Sitagliptin group than in the placebo group [43]. Another short period study, 12 weeks treatment with Sitagliptin resulting in no sustained change in renal function or alteration in renal damages markers [44].

In this work, we found the reduction in renal function was mainly with canagliflozin and Sitagliptin. Based on our and previous studies, one could speculate that the effects of the therapies on renal hemodynamics depend on treatment duration, hyper filtration status, and other population-specific differences.

In this study, Canagliflozin and Sitagliptin were significantly reducing uric acid and this is comparable with many studies. Sodium-glucose co-transporter 2 (SGLT2) inhibitors reduce serum uric acid levels. Serum urate levels were 23.2 μmol/L lower in the canagliflozin versus placebo group at 6 to 13 weeks after randomized study [45]. Regarding Sitagliptin, DPP-4 inhibitors decreased plasma uric acid levels by reducing Xdh expression in adipose tissue but not liver [46].

Conclusion

Canagliflozin, Sitagliptin, and Glimepiride are effective add-on therapy with metformin for proper control of blood glucose in T2DM. Canagliflozin and Glimepiride improve TGs, LDL, and HDL greater than Sitagliptin. Sitagliptin produces less elevation in BUN than Canagliflozin and Glimepiride. Canagliflozin, Sitagliptin or Glimepiride, the results of renal adverse effect was similar for the three drugs used, with the incidence of adverse effect consistent with Canagliflozin.

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