Original Article

Efficacy and Safety of Canagliflozin in Kidney Transplant Patients

Mita Shah, Zaheer Virani, Prashant Rajput, Bharat Shah

Department of Nephrology, Institute of Renal Sciences, Global Hospital, Parel, Mumbai, Maharashtra, India

Abstract

Introduction: There is no report of efficacy and safety of canagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor in post kidney transplant patients with diabetes. **Materials and Methods:** A pilot study was undertaken in stable renal transplant recipients with preexisting diabetes or new onset diabetes after transplantation (NODAT) to look at the efficacy of SGLT2 inhibitor, cangliflozin. With the introduction of canagliflozin (100 mg), the dose of insulin and/or other oral hypoglycemic agents was reduced if the blood sugar control improved. The parameters monitored were body weight, blood pressure (BP), serum creatinine, HbA1c, and tacrolimus trough level. Safety was assessed by adverse event (AE) reports. Each patient was followed for a minimum period of 6 months. **Results:** The study included 24 (23 males and 1 females) stable kidney transplant patients with diabetes. The mean age of the patients was 53.8 ± 7.12 years. The mean body weight of study subjects was 78.6 ± 12.1 kg before and 76.1 ± 11.2 kg 6 months after starting canagliflozin ($P < 0.05$). The mean systolic and diastolic BP (mm Hg) was 142 ± 21 and 81 ± 9 before and 134 ± 17 and 79 ± 8, 6 months after starting canagliflozin, respectively ($P < 0.05$ for systolic BP). There was no significant change in creatinine level (mg/dL). It was 1.1 ± 0.2 before and 1.1 ± 0.3 after starting canagliflozin. The tacrolimus level (ng/mL) was 6.7 ± 3.7 before and 6.1 ± 2, 6 months after starting canagliflozin. The mean HbA1c before was 8.5 ± 1.5%. At 6 months, it was 7.6 ± 1%. Hypoglycemia was not seen. There was no increase in infections. **Conclusion:** Canagliflozin provided reductions in body weight, BP, HbA1c, and the requirement of other hypoglycemic agents without any hypoglycemic episodes and without significant AEs.

Keywords: *Canagliflozin, kidney transplantation, SGLT2 inhibitor, type 2 diabetes mellitus*

Introduction

In healthy individuals, tubules reabsorb most of the glucose filtered by the glomeruli through high-capacity sodium glucose cotransporter 2 (SGLT2) in the early proximal tubule.[1] Normally, about 180 g of glucose is filtered and reabsorbed daily through the kidneys, and the maximal transport rate (Tmax) is 300 mg/min. This rate is about 20% higher, that is, 352 mg/min (19.5 mmol/L/min) to 419 mg/min (23.3 mmol/L/min),[2,3] in patients with poorly controlled type 2 diabetes mellitus (T2DM). This pertains to the increased expression of SGLTs in persons with diabetes, which represents a physiological response to increased glucose delivery to the nephrons that is ultimately maladaptive.[4]

Antagonizing these transporters with SGLT2 inhibitors is an insulin-independent mechanism that offers a considerable advantage of increasing urinary glucose excretion (UGE) without inducing hypoglycemia and promoting weight loss because of loss of 300–400 kcal/day.[5,6]

Canagliflozin is an SGLT2 inhibitor developed for the treatment of patients with T2DM.[7] In Phase 3 studies in patients with T2DM, canagliflozin has been shown to improve glycemic control and reduce body weight and blood pressure (BP) as monotherapy or in combination with a variety of background anti-hyperglycemic agents.[8] Subsequent to that, many studies have shown improved glycemic control with cangliflozin in patients with T2DM. The efficacy and safety of canagliflozin has been reported even in those with chronic kidney disease stage 3.[9] There is only one small case series report of the use of canagliflozin in kidney and simultaneous kidney and pancreas transplant patients. This is another report in the world and the first Indian report of the use of canagliflozin in kidney transplant patients with diabetes mellitus.

How to cite this article: Shah M, Virani Z, Rajput P, Shah B. Efficacy and safety of canagliflozin in kidney transplant patients. Indian J Nephrol 2019;29:278-81.

Address for correspondence:
Dr. Bharat Shah, Institute of Renal Sciences, Global Hospital, Parel, Mumbai, Maharashtra, India.
E-mail: dr_bharatvshah@yahoo.co.in

Access this article online

Website: www.indianjnephrol.org

DOI: 10.4103/ijn.IJN_2_18

Quick Response Code:

Materials and Methods

A pilot study was undertaken in stable renal transplant recipients with preexisting diabetes or NODAT to look at the efficacy of SGLT2 inhibitor, cangliflozin in these patients. Inclusion criteria were stable, willing adult (>18 years), kidney transplant patients with creatinine clearance >60 mL/min, and HbA1c >6.5%. Exclusion criteria were those with unstable creatinine, creatinine clearance <60 mL/min, and alanine aminotransferase level >2.0 times the upper limit of normal (ULN) or total bilirubin >1.5 the ULN. The study also excluded those who had a history of recent urinary tract infection (UTI) or genital mycotic infection. The patients were started on 100 mg of canagliflozin as a fixed dose as per the recommendations.

The parameters monitored were body weight, BP, serum creatinine, estimated creatinine clearance using Cockcroft and Gault's formula, and HbA1c. Follow-up monitoring included following all study patients 2 weekly, monthly, 2 monthly, or 3 monthly depending on their conditions. During each follow-up, weight, BP, self-monitoring of blood glucose (SMBG) values, and creatinine were monitored. HbA1c was monitored 3 monthly. Each patient was followed for a minimum period of 6 months.

Assessment of efficacy and safety

The efficacy of canagliflozin was assessed for change in weight, BP, and HbA1c. Assessments of overall safety and tolerability were based on adverse event (AE) reports such as UTIs, genital mycotic infections, osmotic diuresis, and volume depletion [excessive thirst, weight loss (>5%) in a short span of time, and orthostatic hypotension], and safety laboratory tests. Hypoglycemia episodes included biochemically confirmed episodes. All patients were taught SMBG and were asked to take at least 3 L of liquids.

Statistics

Continuous data are reported as means and standard deviation (SD). Student's paired *t*-test was used to compare the means. Significance of *P* values was defined as values <0.05.

Results

A total of 395 patients of renal transplant with diabetes mellitus were screened and 370 were rejected based on inclusion and exclusion criteria. Thus, the study included 25 (24 males and 1 females) stable, adult (>18 years), kidney transplant patients with creatinine clearance >60 mL/min and HbA1c >6.5%. Twenty patients were diabetic before transplant, and five patients had NODAT. They were on various oral hypoglycemic agent (metformin, sulfonylurea, dipeptidyl peptidase-4 inhibitor, α-glucosidase inhibitor) and/or insulin. They were 3 months to 13 years post-transplant with stable renal function. Canagliflozin was used in the dose of 100 mg/day. With the introduction of canagliflozin, the dose of insulin and/or other oral hypoglycemic agents was reduced. Other concomitant medications of these patients were antirejection medications (tacrolimus, mycophenolate mofetil or azathioprine, and prednisolone), antihypertensive drugs, and lipid lowering agents. One patient discontinued himself after 2 weeks after an insignificant rise in creatinine. Thus, 24 patients were studied [Tables 1 and 2].

The mean body weight soon after transplant was 70.1 ± 11.7 kg. This had increased to 78.6 ± 12.1 kg before starting canagliflozin. After starting canagliflozin, there was soon a trend toward reduction in weight. This continued during the first 6 months of follow-up. Six months after starting canagliflozin, it was 76.1 ± 11.2 kg.

The mean systolic and diastolic BP was 142 ± 21 and 81 ± 9 before and 134 ± 17 and 79 ± 8, 6 months after canagliflozin, respectively ($P < 0.05$ for systolic BP). There was no significant change in creatinine. It was 1.1 ± 0.2 before canagliflozin and 1.1 ± 0.3, 6 months after starting canagliflozin. The mean (SD) creatinine clearance before starting canagliflozin was 86 ± 20, and 6 months after it was 83 ± 18 ($P > 0.05$). The tacrolimus level was 6.7 ± 3.7 before starting canagliflozin and 6.1 ± 2 ng/ml six months after starting canagliflozin. The mean HbA1c before introduction of canagliflozin was 8.5 ± 1.5%. At 6 months, it was 7.6 ± 1%. This was associated with reduction in the requirement of other hypoglycemic drugs. Hypoglycemia was not seen in any case. Three patients felt drained out but felt better after increasing water intake. There was no increase in UTIs or genital mycotic infections.

Discussion

This study examined the efficacy and safety of canagliflozin in kidney transplant patients with T2DM and in those with NODAT. As has been observed in diabetic subjects without kidney disease, there was significant weight loss, small reduction in BP, and significant improvement in glycemic control as judged from HbA1c. The renal function remained stable.

All the patients included in the study had a tendency to gain weight after transplant. Soon after introducing canagliflozin, this trend reversed. In the early period, the weight loss is likely to be because of osmotic diuresis. In the subsequent period, it is likely to be because of caloric loss.[5] With an average of 200–400 calories lost

Table 1: Demographics of study patients

Characteristic	Value
Men/women	23/1
Age (years)	53.8±7.1
BMI (kg/m^2)	28±3.9
Duration of DM (years)	14±8.97
Mean duration of transplant (years)	2.7 (0.2-13.2)

BMI: Body mass index; DM: Diabetes mellitus

Table 2: Mean weight, blood pressure, serum creatinine, and HbA1c before and 6 months after starting canagliflozin

	Baseline	After 6 months	*P*
Weight (kg)	78.6 (12.1)	76.2 (10.9)	<0.05
Systolic BP (mm Hg)	142 (21)	134 (17)	<0.05
Diastolic BP (mm Hg)	81 (9)	79 (8)	>0.05
Serum creatinine (mg/dL)	1.1 (0.2)	1.1 (0.3)	>0.05
Cr Cl (CG formula)	86 (20)	83 (18)	>0.05
HbA1c (%)	8.5 (1.5)	7.6 (1)	<0.05

BP: Blood pressure; Cr Cl: Creatinine clearance; CG: Cockcroft and Gault

per day, weight loss of 2.4–4.7 kg has been demonstrated in 12 week's trial of canagliflozin.[6] We observed a mean weight loss of 2.4 kg. This is significant considering the fact that there was a tendency to gain weight. It is possible that with a higher dose of canagliflozin (300 mg/day), greater weight reduction could have been achieved.

Because of chronic osmotic diuresis caused by glycosuria with increases in 24-h urinary volumes, canagliflozin is associated with small but consistent reductions in systolic and diastolic BP, for example, 6/2 mmHg.[10,11] This provides a further advantage in transplant patients with diabetes, considering the high incidence of cardiovascular disease in diabetic transplant patients. We too observed 8/2 mmHg decrease in BP in our study patients.

The efficacy on glycemic parameters observed with canagliflozin in our subjects was less than that seen in subjects with T2DM who have normal or only mildly impaired renal function. The mean HbA1c before introduction of canagliflozin was 8.5 ± 1.5%. After 6 months, it was 7.6 ± 1%. This is not unexpected because the rate of UGE is related to both plasma glucose concentration and GFR; with lower GFR, the ability of canagliflozin to augment UGE is attenuated.[12] With lesser increases in UGE, the glucose-lowering efficacy of canagliflozin is also reduced. Furthermore, we used only 100 mg dose.

The common side effects described with canagliflozin are increased urination, UTI, and genital mycotic infections. None of these problems were seen in our patient. Consequent to osmotic diuresis effect, increased thirst, orthostatic hypotension, and hypotension may also occur.[13,14] Again, none of these adverse effects was seen in our subjects.

O-glucuronidation is the major metabolic elimination pathway for canagliflozin. It is glucuronidated by UGT1A9 and UGT2B4 to two inactive *O*-glucuronide metabolites M5 and M7.[12] CYP3A4-mediated metabolism of canagliflozin is minimal in humans, hence it is least likely to result in significant drug interactions.[15] The tacrolimus levels were not affected in our subjects.

In summary, canagliflozin was well tolerated by kidney transplant patients with diabetes mellitus. There was significant weight loss, small reduction in BP, and significant improvement in glycemic control. There were no significant side effects, and there was no interaction with immunosuppressive drugs.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Wright EM, Hirayama BA, Loo DF. Active sugar transport in health and disease. J Intern Med 2007;261:32-43.
2. DeFronzo RA, Davidson JA, Del Prato S. The role of the kidneys in glucose homeostasis: A new path towards normalizing glycaemia. Diabetes Obes Metab 2012;14:5-14.
3. Mogensen CE. Maximum tubular reabsorption capacity for glucose and renal hemodynamcis during rapid hypertonic glucose infusion in normal and diabetic subjects. Scand J Clin Lab Invest 1971;28:101-9.
4. Bakris GL, Fonseca VA, Sharma K, Wright EM. Renal sodium-glucose transport: Role in diabetes mellitus and potential clinical implications. Kidney Int 2009;75:1272-7.
5. Komoroski B, Vachharajani N, Boulton D, Kornhauser D, Geraldes M, Li L, *et al*. Dapagliflozin, a novel SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. Clin Pharmacol Ther 2009;85:520-6.
6. Sha S, Devineni D, Ghosh A, Polidori D, Chien S, Wexler D, *et al*. Canagliflozin, a novel inhibitor of sodium glucose co-transporter 2, dose dependently reduces calculated renal threshold for glucose excretion and increases urinary glucose excretion in healthy subjects. Diabetes Obes Metab 2011;13:669-72.
7. Nomura S, Sakamaki S, Hongu M, Kawanishi E, Koga Y, Sakamoto T, *et al*. Discovery of canagliflozin, a novel C-glucoside with thiophene ring, as sodium-dependent glucose cotransporter 2 inhibitor for the treatment of type 2 diabetes mellitus. J Med Chem 2010;53:6355-60.
8. Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K, *et al*. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care 2012;35:1232-8.
9. Yale JF, Bakris G, Cariou B, Yue D, David-Neto E, Xi L, *et al*. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab 2013;15:463-73.
10. Rajasekeran H, Kim SJ, Cardella CJ, Schiff J, Cattral M, Cherney DZI, *et al*. Use of canagliflozin in kidney transplant recipients for the treatment of type 2 diabetes: A case series. Diabetes Care 2017;40:e75-6.
11. List JF, Whaley JM. Glucose dynamics and mechanistic implications of SGLT2 inhibitors in animals and humans. Kidney Int Suppl 2011;120:S20-7.
12. Devineni D, Curtin CR, Polidori D, Gutierrez MJ, Murphy J, Rusch S, *et al*. Pharmacokinetics and pharmacodynamics of canagliflozin, a sodium glucose co-transporter 2 inhibitor, in subjects with type 2 diabetes mellitus. J Clin Pharmacol 2013;53:601-10.
13. Shawaqfeh MS, Bhinder MT, Halum AS, Harrington C, Muflih S, Do T. Adverse drug events related to canagliflozin: A meta-analysis of randomized, placebo-controlled trials. Adv

Pharmacoepidemiol Drug Saf 2015;4:196-202.
14. Wilding JP, Blonde L, Leiter LA, Cerdas S, Tong C, Yee J, *et al*. Efficacy and safety of canagliflozin by baseline HbA 1c and known duration of type 2 diabetes mellitus. J Diabetes Complications 2015;29:438-44.
15. Kaushal S, Singh H, Thangaraju P, Singh J. Canagliflozin: A novel SGLT2 inhibitor for type 2 diabetes mellitus. N Am J Med Sci 2014;6:107-13.