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Use of SGLT2 Inhibitors in Diabetic Renal Transplant Recipients: A Mixed Method Exploratory Exercise

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Chronic kidney disease · Dapagliflozin · Canagliflozin · Empagliflozin · Renal transplant · Physicians' perceptions

Abstract
Background: Diabetes is the leading cause of end-stage renal disease (ESRD) worldwide. Also, diabetes is prevalent in kidney transplant recipients for nondiabetic reasons. ***Methodology:*** We used a mixed method methodology, including a case report, surveys of physicians' opinions, and a review of the literature. ***Results:*** (A) A 58-year-old retired police officer was seen at the diabetes clinic in October 2015. His care was transferred from another physician who had relocated elsewhere. The patient's medical history included type 2 diabetes for over 25 years, hyperlipidemia, hypertension, diabetic neuropathy, diabetic nephropathy, and diabetic retinopathy in addition to vitamin D deficiency and morbid obesity. He had received a renal transplant from a nonrelated live donor 7 years previously. His medications included sitagliptin 50 mg/day, gliclazide (modified release) 60–90 mg/day, metformin (extended release) 750 mg twice daily, and dapagliflozin 10 mg/day. We focus on the off-license use of dapagliflozin in a patient with a history of ESRD and renal transplantation. The lack of published experience with sodium-glucose cotransporter 2 (SGLT2) inhibitors in renal transplant recipients was discussed with him. "But I came to no harm," was his reply. His records on renal function, hydration status, and glycemic control all seemed unaffected over the previous 2.5 years. He remains well till the time of this report. Serum electrolytes, creatinine, plasma albumin, hemoglobin, packed cell volume, and estimated glomerular filtration rate (eGFR) were not adversely affected. Glycated hemoglobin and fasting blood glucose were stable. Urine was consistently negative for ketones but loaded with glycosuria. It was agreed to continue with the same medication, observe the patient carefully, and seek for opinions of other physicians. (B) An online survey was conducted; the responses revealed that many physicians would use SGLT2 inhibitors in renal transplant recipients provided the renal function was satisfactory with an eGFR >60. We have learned of an ongoing trial on SGLT2 inhibitors in renal transplant recipients. (C) A case series of 10 patients treated with canagliflozin showed reassuring findings. ***Conclusions:*** Despite the lack of formal trial evidence, the index case suggested the safe use of SGLT2 inhibitors by renal transplant recipients for a remarkably extended period of 2.5 years. Physicians seem willing to use SGLT2 inhibitors in this group of patients provided renal function is satisfactory.

Introduction

Diabetes is the leading cause of end-stage renal disease (ESRD) worldwide [1]. Renal transplantation is an eventuality for a proportion of patients with ESRD. Also, diabetes is prevalent in kidney transplant (KT) recipients for

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nondiabetic etiology [2]. In this population, specific risk factors associated with the development of diabetes, classed as new-onset diabetes after transplantation (NODAT), include the use of diabetogenic immunosuppressive medications (particularly glucocorticoids), hypomagnesemia, and posttransplant weight gain [3]. Management of hyperglycemia in patients with declining kidney function can be a challenging task with opposing forces leading to hypoglycemia and hyperglycemia coupled with limitations imposed on the use of many antidiabetic medications [4].

In nontransplant populations with type 2 diabetes mellitus (T2DM) and established cardiovascular (CV) disease, the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors has been shown to improve glycemic control, promote weight loss, and reduce the risk of CV events [5]. Diabetes and the high CV burden in transplant recipients make the SGLT2 inhibitor therapy in this population particularly sensible due to the concurrent advantageous effects it offers on hyperglycemia, weight gain, and hypertension [6]. However, data regarding the safety of SGLT2 inhibitors in KT recipients are scarce. This group of patients must obviously have been excluded from registration studies and other trials. The observed drop in estimated glomerular filtration rates (eGFRs), albeit transient, may make physicians particularly wary of their use [7]. However, in the long term, SGLT2 inhibitors may have renal protective effects in people with impaired kidney function [8]. A systematic review and meta-analysis of 40 randomized controlled trials comprising 29,954 patients evaluated the use of SGLT2 inhibitors in people with T2DM with or without renal impairment. Emerging data suggest that with SGLT2 inhibition, renal function seems to be preserved in people with diabetes with or without renal impairment. Furthermore, SGLT2 inhibition prevents further renal function deterioration and death from kidney disease in these patients [8]. In the absence of formal trial evidence, real-world evidence, such as the current report, from inadvertent coincidence and clinicians' perceptions and practices may help shed some light on this issue.

Materials and Methods

The current study aims to benefit from an opportunity that we encountered to gain insight into the uncharted territory of using SGLT2 inhibitors in renal transplant recipients. We use the mixed method approach of a detailed clinical case report, an online survey of physicians' perceptions using 2 platforms, and a focused review of the literature.

The survey of physicians' perceptions was based on a cross-sectional electronic questionnaire conducted using web-based commercial software (Survey Monkey, Palo Alto, CA, USA). The survey was sent to an institutional database of physicians based in the Middle East and Africa. Data were summarized anonymously using descriptive statistics. Results are presented as absolute and relative frequencies (%) to take account of any missing answers. Responses were received from 44 physicians mostly from the Middle East. Fifty percent were endocrinologists, 32% were internists, 61.4% were consultants, and 34.1% were sub-consultant specialists. Physicians were asked the following question: "In a sub-optimally controlled patient with T2DM (with HbA1c 7.9%) who is obese and has a stable renal transplant, would you think (on basis of efficacy and safety) it appropriate to use an SGLT2 inhibitor provided that the patient's eGFR is greater than 60 (i.e., serum creatinine is normal)?"

At the same time, we posted a question on ResearchGate [9]. The research question was: "Would you use SGLT2 inhibitor in a T2DM patient who is a renal transplant recipient and eGFR >60?" (provided that there are no other contraindications). Respondents were asked to address 3 aspects: (1) Is there any trial evidence for efficacy and safety? (2) Do you have any personal experience? (3) Would you dare do it (own view)? Nine responses were received from responders with varying levels of research experiences and clinical backgrounds.

Finally, a focused narrative review of the literature was conducted using the PubMed online database (PubMed, NLM) and the combination of "SGLT inhibitors and renal transplants" as the search terms, and a search for relevant ongoing trials was conducted on the clinicaltrials.gov website.

Results

Case Report

A 58-year-old retired police officer was seen at the diabetes clinic in October 2015. His care was transferred from another physician who had relocated elsewhere. The patient's medical history included T2DM for over 25 years, hyperlipidemia, hypertension, diabetic neuropathy, diabetic nephropathy, and diabetic retinopathy in addition to vitamin D deficiency and morbid obesity. He had received a renal transplant from a nonrelated live donor 7 years previously. His medications included sitagliptin 50 mg/day, gliclazide (modified release) 60–90 mg/day, metformin (extended release) 750 mg twice daily, and dapagliflozin 10 mg/day. The consultation seemed so far typical of what is seen on a daily basis in any diabetic clinic everywhere. However, the use of dapagliflozin with a history of ESRD and renal transplantation was not particularly straightforward. The patient's record was reviewed, and the use of this newer class of drugs was justified by the initiating physician by poor glycemic control on maximal doses of oral agents in a patient who was adamantly refusing insulin therapy.

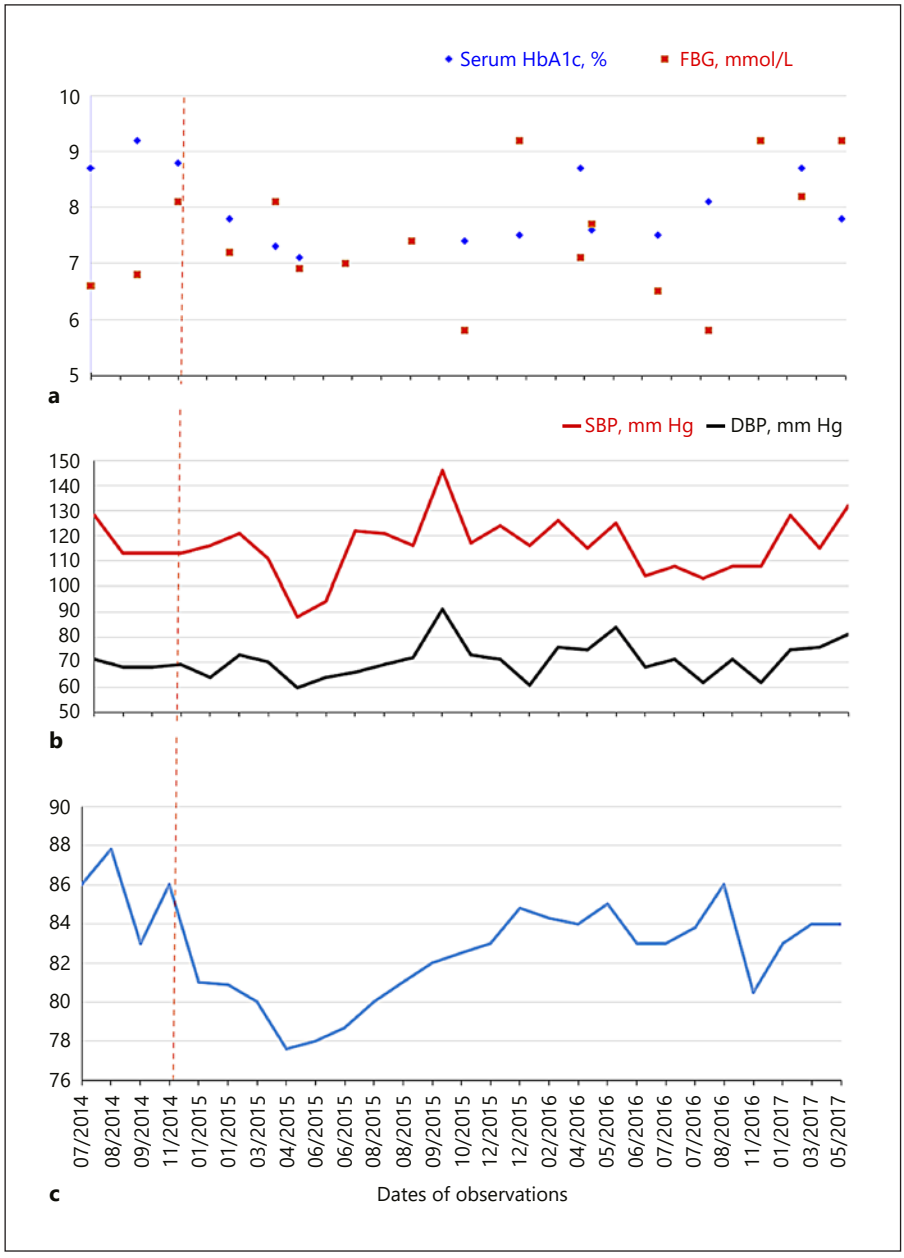

Fig. 1. The trends of glycemic control (expressed as HbA1c and fasting blood glucose) (**a**), SBP and DBP (**b**), and body weight measurements (**c**) recorded in the renal and diabetes clinics before and after the treatment with the SGLT2 inhibitor (dapagliflozin 10 mg daily). The vertical dotted line indicates the start of the SGLT2 inhibitor therapy. Dates shown in section **c** apply to both **a** and **b**. The y-axis in **a** and **b** applies to both variables. HbA1c, glycated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; SGLT2, sodium-glucose cotransporter 2.

The lack of published experience with SGLT2 inhibitors in KT recipients was discussed with the patient. "But I came to no harm," was the patient's reply. Indeed, his records on renal function, hydration status, and glycemic control all seemed unaffected over 2.5 years. These observations revealed that body weight and systolic and diastolic blood pressures decreased transiently slightly after the introduction of dapagliflozin but then rose again. HbA1c and fasting plasma glucose were maintained reasonably (Fig. 1). Urine was consistently negative for ketones but loaded with glycosuria. Serum Na, K, creatinine, and eGFR remained stable. Markers of hemoconcentration and dehydration, i.e., plasma albumin, hemoglobin, and packed cell volume, were not adversely affected (Table 1).

Physicians' Perception and Practices

Of the total 44 respondents, 59.1% use the SGLT2 inhibitor class regularly, and 28% see transplant recipients often. Responses revealed that 20.9% would never use an SGLT2 inhibitor in a renal transplant recipient even if eGFR is >60, whereas 65.1% stated that they would use

SGLT2 inhibitors if renal function is normal (eGFR >60). Those who refrained from the use of SGLT2 inhibitors justified their viewpoint by not wanting to take unnecessary risks in the absence of evidence (52.6%) and stated that other safer options are available (42.1%). Also, patients are mostly on immunosuppressive therapy which may increase the risk of genitourinary tract infections (57.9%). Concern about the risk of dehydration and its impact on renal transplant survival (31.6%) and about the initial reduction in eGFR with this class of drugs (15.8%) has been expressed. Those who were prepared to use SGLT2 inhibitors in this situation (i.e., KT recipients) expressed the opinion that SGLT2 inhibitors have a beneficial effect on hyperglycemia, weight gain, and increased CV risk seen in posttransplant patients (58.8%), as long as eGFR is normal. Also, they thought that transplanted kidneys behave like native kidneys (55.9%); chances of genitourinary tract infections are rare and can be treated with standard therapies (35.3%); theoretically there is no evidence for risk (29.4%), and that volume depletion is actually minimally mild and can be rectified by the intake of extra small amounts of fluids (29.4%).

Nine responses were posted in response to the ResearchGate question [9]. The most notable response was from an expert who shared a personal communication of his involvement in an ongoing trial on SGLT2 inhibitors in KT recipients. A few respondents repeated that there is a lack of experience with chronic kidney disease treatment in diabetic patients. It was highlighted by some respondents that hyperglycemia, as well as hyperinsulinemia, are potent stimulants of inflammation in the kidney, which could further increase the inflammatory response of the already injured KT. Typically, T2DM patients are insulin resistant, which does not mean that they are also resistant to the inflammatory response. Therefore, the use of SGLT2 inhibitors was favored by some respondents instead of insulin to decrease the noxious stimuli of hyperglycemia as well as insulin resistance, attenuating the progression of chronic kidney disease. However, some were concerned about the increased risk of urogenital infections in an immunocompromised patient, especially when the anatomy is distorted in both the native and transplanted kidneys, which might predispose the patient to ascending infections. Some laboratory work was also quoted: phlorizins normalized renal function without further glomerular damage in STZ diabetic rats, insulin normalized glycemia and renal functions but promoted glomerular mesangial expansion. So, there are fewer problems with SGLT inhibitors than with insulin treatment.

Table 1. The biochemical and hematological parameters before (2014) and during the 2.5 years on dapagliflozin (2015–2017) and the daily doses of antidiabetic medications (mg/day)

Data	2014			2015						2016					2017	
	July 1	Sept. 8	Nov. 9	Jan. 7	March 16	May 18	July 22	Sept. 28	Nov. 29	Jan. 28	May 26	June 28	Aug. 28	Oct. 30	Jan. 9	March 1 April 30
Renal function																
Na, mmol/L	139	138	139	138	137	139	138	140	138	136	136	136	139	135	141	140 140
K, mmol/L	4.3	3.9	4.0	4.3	3.8	4.2	4.0	4.1	4.0	3.9	4.2	4.1	4.2	3.8	3.9	4.0 4.1
Cr, μmol/L	81	79	88	87	89	90	85	81	77	81	87	78	78	77	71	81 76
Urea, mmol/L	5.1	2.4	5.5	5.7	5.2	6.1	6.3	5.5	5.1	5.7	6.4	4.5	5.8	–	4.4	5.2 4.9
eGFR	93	97	84	84	82	81	87	92	98	91	84	96	96	97	106	71 59
Markers of hemoconcentration and dehydration																
Alb, g/L	38	38	36	38	32	32	32	35	36	31	34	34	34	34	36	37 33
Hemoglobin, g/L	143	141	140	141	134	133	127	126	128	122	118	118	116	129	131	127 119
HCT, %	43	43	42	43	43	42	41	40	42	40	39	39	38	43	43	42 40
USG	1.015	1.005	1.010	1.015	1.016	–	1.027	–	1.000	1.008	1.011	1.017	1.005	1.020	1.011	1.013 1.011
Medication and doses																
Metformin XR	1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500 1,500
Sitagliptin	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50 50
Gliclazide MR	90–120	90–120	90–120	90–120	90–120	90–120	90–120	90–120	90–120	90–120	90–120	90–120	90–120	90–120	90–120	90–120 90–120
Dapagliflozin	nil	nil	nil	10	10	10	10	10	10	10	10	10	10	10	10	10 10

Cr, creatinine; eGFR, estimated glomerular filtration rate; Alb, albumin; HCT, hematocrit; USG, urinary specific gravity; XR, extended release; MR, modified release.

Discussion

Diabetic nephropathy is the most common cause of ESRD worldwide. Blood glucose and blood pressure control reduce the risk of developing this complication; however, once nephropathy is established, it is only possible to slow progression. SGLT2 inhibitors, the most recent glucose-lowering oral agents, may have the potential to exert nephroprotection not only through improving glycemic control but also through glucose-independent effects, such as blood pressure lowering and direct renal effects. It is important to consider, however, that in patients with impaired renal function, given their mode of action, SGLT2 inhibitors are less effective in lowering blood glucose [10].

When we were faced with the case of this patient, we were sailing an uncharted sea. First of all, we shared our concerns with the patient. Being a retired police officer, he was the sort of "if it ain't broken, do not fix it" type of person. We searched the literature again using Google and PubMed to no avail. A couple of weeks after the first encounter, there was a "stand-alone meeting" sponsored by one of the manufacturers of SGLT2 inhibitors. A question was asked to the eminent international speaker in public if he had any experience with SGLT2 inhibitors in KT recipients. He admitted lack of any experience and simply reiterated the current guidance on eGFR cutoff points [11]. We phrased the question on ResearchGate in a challenging tone, "would you use SGLT2 inhibitor in a T2DM patient who is a KT recipient and eGFR >60?," in an attempt to draw attention to the problem. Most respondents had no personal experience. Concern about infection in the presence of steroids and immunosuppressant therapy and concern about the negative impact on renal function was expressed.

To our knowledge, there are no fully reported trials in diabetic KT patients. Nonetheless, 2 reports are relevant to the present argument [12, 13]. Rajasekeran et al. [12] described a short-term experience with transplant recipients treated with canagliflozin. There were no urinary or mycotic infections diagnosed during treatment. One patient experienced hypoglycemia that did not require hospitalization, and 1 patient developed cellulitis. No patients suffered acute rejection or acute kidney injury. Another study from Korea available in abstract form evaluated the safety and efficacy of an SGLT2 inhibitor in 25 KT patients who were treated with dapagliflozin 5 mg/day [13]. Three patients had type 1 DM, and 7 had NODAT. Sixteen patients were on insulin with or without oral agents. Diuretics were stopped before the initiation of the study drug. Baseline mean HbA1c was 7.9%, and it decreased significantly at 3 and 6 months to 7.4%. Mean body weight was significantly reduced from 72 to 68 kg at 12 months. Two patients stopped insulin, and the other 4 patients could reduce the dose of insulin by ≥20%. eGFR did not change significantly (71.1 ± 20.1 mL/min at baseline, 71.5 ± 25.8 mL/min at 12 months). Clinically apparent acute graft dysfunction was not observed. Office blood pressure also was not improved considerably, but 10 of 24 patients had a decrease in the number and dose of antihypertensives. There was no significant change in the urine albumin-creatinine ratio at 1 year. Six patients discontinued the study drug due to acute cystitis in 2, weight loss in 1, and lack of efficacy in 3. Therefore, the SGLT2 inhibitor in this study seemed to be beneficial in the glucose control of transplant patients, with an acceptable safety profile. Our case report lends support to this case series with a much more extended observation period. Another clinical trial is ongoing at the University of Vienna, Austria [14]. It plans to include 16 patients with stable renal allograft function, stable immunosuppressive therapy, and NODAT, on standard antidiabetic treatment (exogenous insulin <40 IU). The primary endpoint is 2-h blood glucose during an oral glucose tolerance test immediately prior and 1 month after the start of empagliflozin monotherapy. Safety endpoints include clinically concerning hyperglycemia after discontinuation of exogenous insulin, ketoacidosis, urinary tract infections and genital infections, worsening of renal function, hypoglycemia, hospitalizations, CV events, and death. Although this is not an identical clinical situation, its results should provide some useful physiological and mechanistic information.

Given the susceptibility to infectious complications of patients with diabetes and concomitant immunosuppression, clinicians may avoid SGLT2 inhibitors in KT recipients because of their side effects. However, in the 2 reports on this issue, the use of SGLT2 inhibitors was generally well tolerated [12, 13]. Our case report is the longest report of its nature hitherto. An overall improvement in glycemic control, weight, and blood pressure was also observed, which was similar in magnitude to the effects reported in nontransplant cohorts. In our patient, matters are complicated by the poor concordance, complacency, and negative attitude to insulin therapy.

Conclusions

Despite the lack of formal trial evidence, the index case revealed the safe use of SGLT2 inhibitors by renal transplant recipients for an unprecedented extended period of

over 2.5 years. In the survey, physicians seem willing to use SGLT2 inhibitors in this group of patients on a similar basis as in nontransplant patients provided renal function is satisfactory. In the 2 preliminary reports and our case report, SGLT2 inhibitors seem to be beneficial for glucose control of transplant patients, with an acceptable safety profile. There is an urgent need to study this particular clinical scenario more formally by capturing carefully collected data retrospectively or through prospective trials. The full reports of the 2 trials highlighted above are eagerly awaited and should provide a more solid basis for future research and clinical practice. In the interim, practicing physicians should be cautious, treat patients on an individual basis, and make use of the learning opportunity provided by serendipity.

Acknowledgement

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Statement of Ethics

No ethical approval is usually required for individual case reports. However, the patient provided informed consent for anonymous reporting and publication of his history and clinical and biochemical data. Ethical approval was obtained from the institutional review board of Sheikh Khalifa Medical City, Abu Dhabi, UAE, for the survey. All participants provided consent before being able to proceed to the questionnaire. Data were extracted and analyzed anonymously.

Disclosure Statement

The authors report no conflicts of interest.

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No funding was received. In particular, no interaction with the vendors of dapagliflozin occurred. The medication was obtained through the ordinary prescription practices covered by the patient's health insurance scheme.

Author Contributions

S.A.B. conceived the idea of the article. All authors contributed to data collection and examination, revised the manuscript, and approved its final version.

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