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BRIEF COMMUNICATION

Tolerability and efficacy of sodium–glucose co-transporter-2 inhibitors in Australian Aboriginal and Torres Strait Islanders with type 2 diabetes mellitus: an observational study

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Key words
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Abstract

Sodium–glucose co-transporter-2 inhibitors (SGLT2i) have renal and cardiovascular benefits in addition to their glucose-lowering potential. Data on the efficacy and safety of SGLT2i in Australian Aboriginal and Torres-Strait Islanders are lacking. We conducted a single-centre retrospective study assessing the safety and effects on glycaemic control and albuminuria of SGLT2i in Aboriginal and Torres Strait Islander patients with type 2 diabetes mellitus.

A higher prevalence and earlier onset of diabetes mellitus have been reported in the Australian Aboriginal and Torres Strait Islander population compared to the non-indigenous population.[1] There is a twofold increased risk of albuminuria and a tenfold greater rate of end-stage renal disease requiring renal replacement therapy among the Australian Aboriginal and Torres Strait Islander population compared to the general population.[2] Sodium–glucose co-transporter-2 inhibitors (SGLT2i) have emerged as a promising treatment for type 2 diabetes mellitus (T2DM) with demonstrated glucose-lowering, heart failure, cardiovascular and renal benefits.[3,4] The tolerability and efficacy of SGLT2i in the Australian Aboriginal and Torres Strait Islander population, who have not been well represented in major clinical trials, have not been studied. A cautious approach is currently recommended while using these agents in the Aboriginal and Torres Strait Islander population due to the possibility of an increased risk of urogenital infections, dehydration and the increased risk of diabetic ketoacidosis (DKA).[5]

We conducted a single-centre retrospective study between March 2020 and March 2021, including all Aboriginal and Torres Strait Islander patients with T2DM, aged ≥18 years treated with a SGLT2i attending the Northern Adelaide Local Health Network Diabetes Centre at Watto Purrunna Aboriginal Primary Health Care (WPAPHC) Service. The aim of our study was to assess the side-effect profile, effects on glycaemic control and microalbuminuria of SGLT2i in Aboriginal and Torres Strait Islander patients with T2DM. Patients with type 1 diabetes mellitus and those pregnant were excluded. Body mass index (BMI), blood pressure, glycated haemoglobin (HbA1c) and urine albumin creatinine ratio (UACR) were analysed at baseline and 6–8 months after initiation of SGLT2i. BioGrid Clinical Consultation and database tool and OACIS database were used for data collection. With the exception of laboratory parameters which were manually extracted and then analysed from the OACIS database, all other parameters were extracted and then analysed using BioGrid database software. Ethics approval was sought from the Aboriginal Health Research Ethics Committee and the Southern Adelaide Clinical Human Research Ethics Committee. The project was also discussed with the local Aboriginal and Torres Strait Islander Consumer Reference Group prior to commencement. Data are represented as mean ± standard deviation for continuous

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Table 1 Discontinuation rate and reasons for discontinuation of SGLT2i

Reason for discontinuation	Number of patients *n*/89 (%)
Number of patients	8 (9)
eGFR <45 mL/min/1.73 m^2	2 (2)
Polyuria	1 (1)
Urinary tract infection	1 (1)
Vaginal candidiasis	1 (1)
Active diabetic foot ulcer	1 (1)
Rash and diarrhoea	1 (1)
Unknown reason	1 (1)

variables and median (interquartile range) if not normally distributed. Categorical variables are denoted as the number and percentage of the sample. Statistical analysis was performed using IBM SPSS version 29. Changes in the variables from baseline to 6–8 months after initiation of SGLT2i were analysed by paired *t*-test if normally distributed and Wilcoxon signed-rank test if distribution was not normal.

Two hundred and forty-two Aboriginal and Torres Strait Islanders with T2DM attended WPAPHC in the study period, of which 89 (37%) were prescribed a SGLT2i. Mean age of the cohort was 52 ± 12.8 years, and 39 (44%) were women. Only 8 (9%) patients discontinued SGLT2i during the study period; the reasons for discontinuation are described in Table 1. Fifty-five (62%) of the 89 patients were initiated on a SGLT2i during the study period and also had a follow-up appointment documented at 6–8 months. A repeat HbA1c, BMI and SBP were available at 6–8 months in all 55 patients. Only 39 patients had UACR and 40 patients had estimated glomerular filtration rate (eGFR) documented at 6–8 months' follow-up. Twenty-one out of these 55 patients were also using an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). Patients treated with a SGLT2i had a 1.3% (14.2 mmol/mol) reduction in HbA1c ($P < 0.01$) and a 42% reduction in UACR at 6–8 months ($P = 0.06$; Table 2). A reduction in BMI and systolic blood pressure (SBP) was also noted, as highlighted in Table 2.

Discussion

Our findings highlight the tolerability and safety of SGLT2i in Aboriginal and Torres Strait Islander patients with T2DM. Only eight patients in our study out of the 89 treated with a SGLT2i discontinued treatment. Thirty-seven per cent of T2DM patients attending the WPAPHC service during the study period were prescribed an SGLT2i. The prescription rate of 37% in the Aboriginal and Torres Strait Islander patients with T2DM in our cohort is higher when compared to that reported in the primary healthcare setting in Australia in 2017[6] and is in keeping with the reported increasing trend in SGLT2i use.[7] No patients treated with SGLT2i developed DKA. Our cohort had a low incidence of urogenital infections that necessitated discontinuation of SGLT2i. Euglycaemic ketoacidosis associated with SGLT2i use has been reported in the literature; however, the event rates in these studies were low.[8,9] Guidelines describing strategies for monitoring and minimising the risk of this complication have been published.[10] The increased risk of urogenital infections with SGLT2i among users is also well documented in various clinical trials.[3,11,12] Even though there were no cases of DKA observed in our cohort, we acknowledge that our sample size was too small to assess whether the incidence of this uncommon adverse event was any different to that reported in other populations. The two patients in whom SGLT2i were discontinued due to a reduction in eGFR to <45 mL/min/1.73 had a 35% and 27% reduction in their eGFR from baseline (eGFR 40 and 48 mL/min/1.73 m^2 at baseline to 26 and 35 mL/min/1.73 m^2 respectively). Both these patients were using an ACEI, and one of them was using a diuretic as well. The renal function in these patients remained stable on follow-up. Since the completion of our study, SGLT2i are now approved for treatment of T2DM in patients with more advanced stages of chronic kidney disease.[13] None of the patients in our cohort experienced severe hypoglycaemia or volume depletion. Our data suggest that with adequate patient education, SGLT2i are safe in Australian Aboriginal and Torres Strait Islander patients with T2DM.

Commencement on SGLT2i was associated with a 42% reduction in UACR in our cohort, which is in

Table 2 Change in variables 6–8 months after initiation of SGLT2i

Sample size (*n*/89)	Variable	Baseline	Follow up	Change from baseline	*P*-value
55	HbA1c, % (mmol/mol)	9.3 ± 2.0 (78.6 ± 20.6)	8.0 ± 1.8 (64.4 ± 19.8)	−1.3 (−14.2)	<0.01
39	UACR (mg/mmol)†	6.37 (0.95–32)	3.70 (1.1–17)	−2.67 (42%)	0.06
40	eGFR (mL/min/1.73 m^2)	89 ± 23	82 ± 23	−7 (7.9%)	<0.01
55	Weight (kg)	99 ± 19	97 ± 18	−2 (2%)	<0.01
55	BMI (kg/m^2)	33 ± 14	32 ± 9	−0.9 (1.2%)	<0.01
55	SBP (mmHg)	128 ± 12	125 ± 12.6	−3 (2.3%)	<0.01

Data are in mean ± SD. †Median (IQR).

keeping with published clinical trials.[14] A reduction in BMI and improvement in SBP in keeping with current evidence[12] were also noted in our cohort (Table 1). A twofold increased risk of albuminuria has been documented in Aboriginal and Torres Strait Islanders compared to the general population, and diabetic nephropathy accounts for 45% of end-stage renal failure in this population compared to 17% in the general population.[5] SGLT2i are reno-protective, with up to a 41% reduction in albuminuria, reduction in progression of end-stage renal disease and mortality demonstrated in clinical trials.[9] Early introduction of these agents in Aboriginal and Torres Strait Islander patients with diabetic nephropathy can delay the progression of renal disease and has the potential to reduce the mortality from chronic renal disease. SGLT2i are now indicated for the treatment of heart failure with reduced left ventricular function and chronic kidney disease independent of diabetes status, both conditions more prevalent in the Aboriginal and Torres Strait Islander community, likely leading to more widespread prescribing of these agents.[15,16]

It is important to acknowledge that our study has several limitations, including the retrospective study design. We also acknowledge the small sample size and limited data availability on follow-up. However, to our knowledge, no studies have been published assessing the safety profile of SGLT2i in the Australian Aboriginal and Torres Strait Islander population. Our study provides important insight into the safety, renal and cardio-metabolic benefits of SGT2i in Aboriginal and Torres Strait Islander population. Larger studies are required to assess further the benefits of SGLT2i in Aboriginal and Torres Strait Islander population with T2DM, including its role in the primary prevention of cardio-renal complications associated with diabetes mellitus.

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