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The effect of Ramadan fasting and continuing sodium-glucose co-transporter-2 (SGLT2) inhibitor use on ketonemia, blood pressure and renal function in Muslim patients with type 2 diabetes

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ABSTRACT

Objective: The effect of Ramadan fasting and continuing sodium-glucose co-transporter-2 (SGLT2) inhibitor use on ketonemia, blood pressure and renal function in Muslim patients with type 2 diabetes.

Methods: This is a single-centre prospective observational controlled cohort study. Muslim patients aged 21–75 years with type 2 diabetes and estimated glomerular filtration rate (eGFR) $\geq$ 45 ml/min/1.73 m^2 were eligible if they had no contraindication to observe Ramadan fasting. Patients in study group were on stable dose of SGLT2 inhibitor for at least 3 months before enrolment and continued during study period, while patients in control group were not on SGLT2 inhibitor before and during study period. All participants attended baseline visit before Ramadan and follow-up visit during Ramadan.

Results: A total of 68 patients of similar baseline characteristics were included in the study: 35 in study group and 33 in control group. During Ramadan fasting, patients from study and control group had similar change in weight (LS mean change of −1.8 versus −1.1 kg, p = 0.205), eGFR (LS mean change of −6.0 versus −4.2 ml/min/1.73 m^2, p = 0.399), sitting systolic BP (LS mean change of −8.1 versus −10.4 mmHg, p = 0.569), sitting diastolic BP (LS mean change of −3.7 versus −3.5 mmHg, p = 0.934) and plasma β-hydroxybutyrate level (LS mean change of −0.01 versus −0.02 mmol/L, p = 0.649).

Conclusions: Ramadan fasting was associated with significant changes in weight, BP and eGFR regardless whether patients were on SGLT2 inhibitor treatment. Continued use of SGLT2 Inhibitors during Ramadan did not increase ketonemia, nor increase risk of eGFR deterioration and hypoglycaemia.

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1. Introduction

Abstinence from food and drink from dawn till dusk is an integral part of observing Ramadan for healthy adult Muslims worldwide. The Epidemiology of Diabetes and Ramadan (EPIDIAR) study and CREED study reported that about 3 out of 4 Muslim patients with type 2 diabetes fasted during Ramadan globally [1,2]. Although Ramadan fasting can result in favorable physiological changes such as decreased body weight and improved lipid profile [3,4], patients with diabetes during Ramadan fasting are at higher risk for complications such as hypoglycemia, hyperglycemia, dehydration and diabetic ketoacidosis [1,2].

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are the newest class of oral anti-diabetic drugs (OADs) which lower blood glucose by inhibiting renal glucose reabsorption and increasing urinary glucose excretion. SGLT2 inhibitors have demonstrated its effectiveness in glycemic control with beneficial weight reduction without increased risk of hypoglycemia in several trials [5–7]. The recently published EMPA-REG and CANVAS trials reported additional benefits of SGLT2 inhibition on cardiovascular and renal outcomes among patients with type 2 diabetes at high cardiovascular risk [8,9]. Thus, there has been an increase in SGLT2 inhibitor use in recent years and this is expected to rise further over time. SGLT2 inhibitors generally have a good safety profile when used in patients with type 2 diabetes [5–9]. However, the risk of ketoacidosis and dehydration associated with SGLT2 inhibitor use could be potentiated during Ramadan fasting and become a safety concern. To date, the available evidence on the safety of SGLT2 inhibitor use during Ramadan fasting is limited [10–12].

There is a large Malay-Muslim population in Singapore (~0.8 million), of whom an estimated 16.6% have type 2 diabetes [13]. With the introduction and rapidly increasing use of SGLT2 inhibitors in Singapore, its safety especially from the perspective of increased ketonemia and possible increase in incidence of clinical ketoacidosis when used during Ramadan requires further study. Hence, we undertook this study to evaluate the safety of continuing SGLT2 inhibitor during Ramadan fasting in Muslim patients with type 2 diabetes.

2. Research design and method

2.1. Subjects and study design

This was a single-centre, prospective, observational controlled cohort study, conducted from April to June 2017 at a tertiary hospital diabetes centre in Singapore. Muslim patients aged 21–75 years with type 2 diabetes and estimated glomerular filtration rate (eGFR) $\geq$ 45 ml/min/1.73 m^2 were eligible for inclusion if they intended to and had no contraindication to observe Ramadan fasting. An additional inclusion criterion for study group patients was that they had been on stable doses of SGLT2 inhibitors for at least 3 months while control group patients were not on SGLT2 inhibitor prior to enrollment. SGLT2 inhibitor therapy in this study refers to any drug and dose of SGLT2 inhibitor class that patients were receiving, which could be used as monotherapy or in combination with other OADs and insulin. During the study period, all patients from the study group needed to be maintained on SGLT2 inhibitors while all control group patients should not be initiated on SGLT2 inhibitors. Exclusion criteria in this study were: type 1 diabetes, eGFR < 45 ml/min/1.73 m^2, pregnancy and ongoing glucocorticoid use.

The study was reviewed and approved by the institutional review board. Data from electronic clinical databases and written medical records of Muslim patients on follow-up at the Diabetes Centre were reviewed to confirm their eligibility and to categorize them into either study group or control group according to the recruitment criteria. All participants in the study were required to attend baseline visit (within 2 months before Ramadan) and follow-up visit during Ramadan for clinical assessment and data collection. All participants provided written informed consent.

2.2. Study end-points and assessment

Participants from both groups had fasting plasma β-hydroxybutyrate and renal panel with plasma glucose measured at baseline visit after overnight fasting and again during Ramadan visit before sunset meal (Iftar). The primary endpoint in this study was the change from baseline in fasting plasma β-hydroxybutyrate level measured after 8–10 h of fasting. For the fasting plasma β-hydroxybutyrate at Ramadan visit, all participants were required to have completed at least 1 week of Ramadan fasting before the test. Plasma ß-hydroxybutyrate (Cayman Chemical Company, Ann Arbor, U.S.A) was measured in duplicates. A level of $\geq$0.60 mmol/L was deemed to indicate clinically significant ketonemia in the study [14].

Secondary end-points in the study were the change from baseline in weight, blood pressure (BP), fasting plasma glucose and eGFR. Pre-specified adverse events include incidence of hypoglycemia, postural hypotension and acute kidney injury (AKI). Patients in the study performed self-blood glucose monitoring during Ramadan as advised by their primary doctor. Hypoglycemia in the study was defined by any reported symptomatic or documented (blood glucose level $\leq$ 3.9 mmol/L) hypoglycemic event in the previous week. Severe hypoglycemia was defined as hypoglycemia requiring assistance of another person for treatment or resulting in loss of consciousness/seizures. Postural hypotension was defined as a fall in systolic BP of at least 20 mmHg or diastolic BP of at least 10 mmHg when a person assumes a standing position from a sitting position.

2.3. Statistical analyses

The primary analysis in this study was to compare fasting plasma β-hydroxybutyrate level measured before and during Ramadan, for patients using versus not using SGLT-2 inhibitors. The mean difference and standard deviation (SD) of plasma ß-hydroxybutyrate levels in patients with versus without chronic use of SGLT2 inhibitor reported in a previous study was used to estimate sample size [15]. It was estimated that 35 subjects in each group would provide a power of 80% with a significance level of 5%.

Baseline characteristics of study group and control group were compared using t-tests or chi-square tests as appropri-

ate. Least squares (LS) mean change in key measurements such as weight, BP, eGFR, fasting plasma glucose, fasting plasma ß-hydroxybutyrate between baseline and Ramadan visit were compared across study and control groups. Proportion of patients with adverse events at baseline and Ramadan visit was compared within same treatment group using McNemar' tests, and was compared between the two groups using Chi-square tests. Statistical analysis in the study was performed using STATA Data Analysis and Statistical Software. All statistical tests used in the study were two-sided and considered significant if $P < 0.05$.

3. Results

3.1. *Subject disposition and baseline characteristics*

A total of 68 patients who met inclusion criteria were recruited into the study, 35 in the study group and 33 in the control group. Thirty -three patients (94.3%) from the study group and 29 (87.9%) from the control group successfully completed the study. For the patients in the study group who completed the study, 19 were on full dose of canagliflozin or empagliflozin, and 14 patients were on partial dose of canagliflozin or empagliflozin. Among the 6 patients who did not attend Ramadan visit, 2 patients were admitted prior to the start of Ramadan: 1 patient from control group was admitted for scar epilepsy and the other patient from study group was admitted for gouty arthritis. The other 4 patients cited busy schedule as the reason.

Demographic and biochemical characteristics of patients at baseline were generally similar between the two treatment groups except for body weight (Table 1). Overall mean age of patients was 52.2 ± 11.1 years, duration of diabetes 14.1 ± 7.4 years, body mass index (BMI) 31.8 ± 7.9 kg/m^2, mean baseline HbA1c 9.0 ± 1.8%, eGFR 88.2 ± 22.8 ml/min/1.73 m^2, and median urine albumin-to-creatinine ratio 60.0 (19.0–218.0) μg/mg. Approximately half of the patients were male in both groups.

Among the study group patients, SGLT2 inhibitors were all used in combination with other anti-diabetic agents including insulin and sulphonylureas. Although not statistically significant, the proportion of patients on insulin therapy was higher in the study group (71.4% versus 54.6%, $p = 0.149$), while proportion of patients on sulphonylureas was higher in the control group (60.6% versus 37.1%, $p = 0.053$) (Table 1). Proportion of patients using premix insulin regimen, glipizide and dipeptidyl peptidase-4 inhibitors was statistically different between control and study group (Table 1). During the study period, all patients from both groups were maintained on their usual anti-diabetic treatment with only adjustments in dose and/or timing for Ramadan fasting. Approximately 48.6% of patients in the study group and 66.7% in the control group were on either ACE inhibitors or angiotensin II receptor blockers ($P = 0.132$).

3.2. *Ketonemia/acidosis*

Patients from both groups observed Ramadan fasting for a mean of 15 days before Ramadan clinic visit. At baseline, patients from the study group had numerically higher although not statistically significant fasting plasma β-hydroxybutyrate level than in the control group (0.31 versus 0.24 mmol/L, $P = 0.076$). At Ramadan visit, patients from both study and control groups had no significant change from baseline in plasma β-hydroxybutyrate level (LS mean change of −0.01 versus −0.02 mmol/L, $P = 0.649$) and bicarbonate level (LS mean change of 0.52 versus −0.05 mmol/L, $p = 0.177$) (Table 2). Only one patient from the study group had plasma β-hydroxybutyrate level > 0.60 mmol/L at Ramadan visit, increasing from 0.53 mmol/L at baseline to 0.69 mmol/L at Ramadan visit. Although the reading was above the defined normal range, this patient was clinically well and had no significant abnormalities in other clinical parameters. He was continued on SGLT2 inhibitor therapy uneventfully during Ramadan.

3.3. *Volume-related parameters and electrolytes*

The study group patients had greater weight reduction at Ramadan visit, but the difference in change between two treatment groups was not significant (LS mean change of −1.8 versus −1.1 kg, $p = 0.205$) (Table 2). Weight reduction from baseline could likely be attributed to both reduced caloric intake and volume loss during Ramadan fasting. Patients from study and control group had similar reduction in both sitting systolic BP (LS mean change of −8.1 versus −10.4 mmHg, $P = 0.569$) and sitting diastolic BP (LS mean change of −3.7 versus −3.5 mmHg, $p = 0.934$) (Table 2). At Ramadan visit, about one third of patients from both the study and control group had reduction in sitting systolic BP of ≥20 mmHg compared to baseline (30.3% versus 37.9%, $p = 0.527$) (Table 3). However, no patient from either group had significant postural BP change at both baseline and Ramadan visit.

In the study group, 5 patients (14.3%) at baseline and 3 patients (8.6%) at Ramadan visit reported symptom of postural giddiness. In the control group, 1 patient (3.0%) had postural giddiness at both baseline and Ramadan visits. All patients with reported postural giddiness in both groups did not have hypotension, nor had any significant postural drop in BP.

Patients from the study group had a greater reduction in eGFR from baseline at Ramadan visit, but the difference in change between the two treatment groups was not statistically significant (LS mean change of −6.0 versus −4.2 ml/min/1.73 m^2, $p = 0.399$) (Table 2). About one quarter of patients from both study and control group had eGFR reduction of ≥10 ml/min/1.73 m^2 at Ramadan visit (27.3% versus 27.6%, $p = 0.978$). One patient from the control group had urinary tract infection at time of Ramadan visit and her serum creatinine increased by 68% from baseline, which returned to baseline after outpatient treatment of UTI and discontinuing the fast.

At Ramadan visit, both study and control group had increase in serum potassium compared to baseline visit (LS mean change of 0.31 versus 0.22 mmol/L, $p = 0.498$) (Table 2). Four (12.1%) and 3 (10.3%) patients from the study and control group respectively, had serum potassium level between 5.5 and 6 mmol/L at Ramadan visit ($p = 0.825$) (Table 3). while none of the patients from either group had potassium ≥5.5 mmol/L at baseline. There was a positive correlation between the increase in serum potassium and eGFR reduction ($r = 0.358$, $p = 0.004$) (data not shown).

Table 1 – Patient baseline characteristics (pre Ramadan) stratified by SGLT2 inhibitor use.

Variable	All	SGLT2 inhibitor		
		No	Yes	p-value
N (%)	68	33 (48.5)	35 (51.5)	
Age (years)	52.2 ± 11.1	54.7 ± 11.2	49.9 ± 10.6	0.075
Male (%)	37 (54.4)	18 (54.6)	19 (54.3)	0.983
Ethnicity (%)				0.429
Indian	7 (10.3)	2 (6.1)	5 (14.3)	
Malay	61 (89.7)	31 (93.9)	30 (85.7)	
DM duration (years)	14.1 ± 7.4	12.3 ± 6.0	15.7 ± 8.3	0.060
Weight (kg)	81.3 ± 22.8	73.9 ± 19.1	88.2 ± 24.1	0.009
BMI (kg/m^2)	31.8 ± 7.9	30.0 ± 8.3	33.4 ± 7.3	0.075
SBP sitting (mmHg)	140.1 ± 19.8	142.7 ± 19.6	137.7 ± 20.0	0.301
DBP sitting (mmHg)	80.5 ± 9.8	82.0 ± 10.8	79.1 ± 8.6	0.221
SBP standing (mmHg)	140.3 ± 21.2	140.8 ± 22.0	139.7 ± 20.7	0.836
DBP standing (mmHg)	81.5 ± 12.2	81.5 ± 14.1	81.6 ± 10.4	0.954
HbA1c (%)	9.0 ± 1.8	8.7 ± 1.6	9.3 ± 1.9	0.192
FPG (mmol/L)	9.7 ± 3.8	10.1 ± 3.9	9.3 ± 3.6	0.348
β-hydroxybutyrate (mmol/L)	0.28 ± 0.16	0.24 ± 0.15	0.31 ± 0.16	0.076
eGFR (ml/min/1.73 m^2)	88.2 ± 22.8	84.9 ± 23.7	91.2 ± 21.8	0.256
Urinary ACR (ug/mg)	60.0 (19.0–218.0)	82.5 (22.0–198.5)	55.0 (17.0–376.0)	0.874
Urinary ACR category (%)				0.451
Normoalbuminuria	20 (30.3)	9 (27.3)	11 (33.3)	
Microalbuminuria	29 (43.9)	17 (51.5)	12 (36.4)	
Macroalbuminuria	17 (25.8)	7 (21.2)	10 (30.3)	
Insulin (%)	43 (63.2)	18 (54.6)	25 (71.4)	0.149
Basal only (%)	22 (32.4)	13 (39.4)	9 (25.7)	0.228
Basal bolus (%)	5 (7.4)	1 (3.0)	4 (11.4)	0.357
Premix (%)	16 (23.5)	4 (12.1)	12 (34.3)	0.045
Sulphonylurea (%)	33 (48.5)	20 (60.6)	13 (37.1)	0.053
Glipizide (%)	28 (41.2)	18 (54.5)	10 (28.6)	0.030
Gliclazide (%)	4 (5.9)	2 (6.1)	2 (5.7)	1.000
Glimepride (%)	1 (1.5)	0 (0.0)	1 (2.9)	1.000
Metformin (%)	62 (91.2)	31 (93.9)	31 (88.6)	0.435
DPP4 inhibitors (%)	13 (19.1)	10 (30.3)	3 (8.6)	0.031
ACE inhibitors or ARB (%)	39 (57.4)	22 (66.7)	17 (48.6)	0.132
Diuretic (%)	6 (8.8)	4 (12.1)	2 (5.7)	0.421

Data presented as mean ± standard deviation; median with interquartile range; number and percentage as appropriate.
SGLT2 inhibitors: sodium-glucose co-transporter 2 inhibitors; DM: diabetes mellitus; BMI: body mass index; HbA1c: glycated haemoglobin A1c; FPG: fasting plasma glucose; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; DPP4 inhibitors: dipeptidyl peptidase-4 inhibitors; ACR: albumin-to-creatinine ratio; ACE inhibitor: angiotensin-converting-enzyme inhibitor; ARB:angiotensin II receptor blockers.

Both serum potassium elevation and eGFR reduction at Ramadan visit had no association with background use of ACE inhibitors or angiotensin II receptor blockers (data not shown).

3.4. *Fasting plasma glucose and hypoglycemia*

Baseline fasting plasma glucose in study group was lower than control group (9.3 versus 10.1 mmol/L, $P = 0.348$) (Table 1). At Ramadan visit, there was an increase in fasting plasma glucose in the study group but a decrease in the control group (LS mean change of 0.35 versus −1.17 mmol/L, $P = 0.102$). Hence, mean fasting plasma glucose level during Ramadan visit was higher in the study group than control group (9.9 versus 8.5 mmol, $P = 0.173$) (data not shown).

Overall, about 60% of patients who were on sulphonylurea and/or insulin therapy had dose and timing adjusted for Ramadan fasting, with no significant difference between the two treatment groups. As compared to pre-Ramadan, although not statistically significant, the proportion of patients experiencing at least one hypoglycemic event during Ramadan fasting increased in the control group (12.1–20.7%, $P = 0.289$), but decreased in the study group (22.9–15.4%, $P = 0.687$). Seven patients from control group and 6 patients from study group were on both sulphonylurea and insulin therapy during the study period. One patient from the control group reported symptomatic hypoglycaemia at both baseline and Ramadan visit; another patient from study group reported symptomatic hypoglycaemia at baseline visit but not at Ramadan visit. One limitation of hypoglycemia assessment in this study was that about half of reported symptomatic hypoglycemia was not confirmed by blood glucose testing. Both groups did not report any incidence of severe hypoglycaemia.

Table 2 – Change in body weight, blood pressure, eGFR, and biochemical values from baseline at ramadan visit stratified by SGLT2 inhibitor use.

Variable	No SGLT2 inhibitor		SGLT2 inhibitor		p-value
	LS mean change (±SE)	95%CI	LS mean change (±SE)	95%CI	
Weight (kg)	−1.1 (±0.4)	−1.9 to −0.3	−1.8 (±0.4)	−2.5 to −1.1	0.205
BMI (kg/m^2)	−1.2 (±0.8)	−2.8 to 0.3	−1.2 (±0.7)	−2.7 to 0.2	0.997
SBP sitting (mmHg)	−10.4 (± 3.0)	−16.4 to −4.4	−8.1 (±2.8)	−13.7 to −2.5	0.569
DBP sitting (mmHg)	−3.5 (±1.4)	−6.4 to −0.7	−3.7 (±1.3)	−6.3 to −1.0	0.934
eGFR (ml/min/1.73 m^2)	−4.2 (±1.6)	−7.3 to −1.1	−6.0 (±1.5)	−8.9 to −3.1	0.399
FPG (mmol/L)	−1.17 (±0.66)	−2.48 to 0.14	0.35 (±0.61)	−0.88 to 1.57	0.102
β-hydroxybutyrate (mmol/L)	−0.02 (±0.01)	−0.05 to 0.01	−0.01 (±0.01)	−0.04 to 0.01	0.649
Creatinine (umol/l)	6.09 (±2.18)	1.73–10.45	6.98 (±2.04)	2.90–11.06	0.769
Potassium (mmol/L)	0.22 (±0.09)	0.03–0.41	0.31 (±0.09)	0.13–0.49	0.498
Sodium (mmol/L)	1.52 (±2.48)	−3.46 to 6.49	−1.07 (±2.28)	−5.65 to 3.50	0.452
Bicarbonate (mmol/L)	−0.05 (±0.30)	−0.65 to 0.56	0.52 (±0.28)	−0.03 to 1.08	0.177
Urea (mmol/L)	0.13 (±0.23)	−0.33 to 0.59	0.20 (±0.21)	−0.22 to 0.62	0.821
Anion gap	1.46 (±1.06)	−0.65 to 3.57	0.79 (±0.97)	−1.15 to 2.74	0.647

Least squares (LS) mean change adjusted for age, gender and baseline parameter of interest.
BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; FPG: fasting plasma glucose.

Table 3 – Adverse events during Ramadan stratified by SGLT2 inhibitor use.

Variable	No. (%)		p-value
	No SGLT2 inhibitor (n = 29)	SGLT2 inhibitor (n = 33)	
Drop in sitting SBP from baseline visit (≥20 mmHg)	11 (37.9)	10 (30.3)	0.527
Drop in eGFR from baseline visit (≥10 ml/min/1.73 m^2)	8 (27.6)	9 (27.3)	0.978
Hyperkalemia at Ramadan visit (≥5.5 mmol/L)	3 (10.3)	4 (12.1)	0.825

Data presented as number and percentage.
SGLT2 inhibitors: sodium-glucose co-transporter 2 inhibitors; SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate.

4. Discussion

Worldwide, many Muslims with type 2 diabetes are receiving or may receive SGLT2 inhibitors to improve glycemic control and other health outcomes. At the same time, most Muslims with diabetes are keen to observe fasting during Ramadan even though many of them are eligible for exemption medically [1,2]. Despite the fact that both Ramadan fasting and SGLT2 inhibitors use can together potentiate the risk of dehydration and ketoacidosis, there is limited available evidence on the safety of SGLT2 inhibitor use during Ramadan fasting. In this prospective cohort study with patients not on SGLT2 inhibitor therapy as the comparator group, we assessed if continued use of SGLT2 inhibitor among Muslims with type 2 diabetes during Ramadan could aggravate health risks such as ketonemia, hypoglycemia and dehydration.

Due to its mechanism of action, SGLT2 inhibitors may predispose patients to ketoacidosis especially in the setting of having other precipitating factors such as acute illness or other stressful conditions [16,17]. In our study, continued use of SGLT2 inhibitor during Ramadan was not shown to increase risk of ketosis as patients from both study and control group had no significant change in plasma β-hydroxybutyrate level at Ramadan visit. No patient from either group developed clinical ketoacidosis during the study period.

Continued use of SGLT2 inhibitor during Ramadan did not increase risk of hypoglycemia in our study. In fact, the proportion of patients experiencing at least one hypoglycemic event during Ramadan fasting increased in the control group numerically, but decreased in the study group. This is likely related to the insulin-independent glucose-lowering action of SGLT2 inhibitor, consistent with findings from previous studies [10,11].

Patients from both study and control group had similar statistically significant reduction in weight, BP and eGFR from baseline during Ramadan visit. Serum potassium increased in both groups at Ramadan visit. This was correlated to the reduction in eGFR but not background use of ACE inhibitors or ARBs. To our knowledge, our observations on BP and eGFR changes during Ramadan are novel and have not been previously reported, implying that Ramadan fasting itself can bring about non-trivial relative dehydration regardless of whether patients are on SGLT2 inhibitor treatment or otherwise. It is unclear at the moment whether such relative dehydration, if repeated during yearly Ramadan fasting, may contribute towards development and progression of kidney disease in the setting of diabetes. However, separately there is evidence in the literature that more severe forms of insult to the kidney resulting in AKI increases the risk of advanced CKD in patients with diabetes independent of other major risk

factors of kidney disease, and that each episode of AKI doubles the risk [18].

One limitation of the study is that its sample size was slightly smaller than what was estimated to provide adequate power. This is due to the logistical challenge of getting participants to agree to attend the second clinic visit with venepuncture during Ramadan itself. Accurate assessment of fluid intake and loss before and during Ramadan visit in the outpatient setting was not possible. Hence it was not possible to provide a quantitative perspective on fluid balance and its role in the causation of dehydration and eGFR deterioration during Ramadan. This study was originally powered to study the effect of Ramadan fasting and continuing SGLT2 inhibitor use during Ramadan on ketonemia in Muslim patients with type 2 diabetes. However, as we observed significant changes in BP and eGFR during the study, we felt compelled to report these findings. Hence, these findings should at best be considered preliminary. Overall, participants in this study were at lower risk for fasting-related complications in view of their relatively young age, good kidney function and few significant comorbidities. It is thus not possible to extrapolate the findings to a higher risk population.

In summary, findings from our study showed that continued use of SGLT2 Inhibitor treatment during Ramadan in patients with type 2 diabetes receiving stable dose of SGLT2 inhibitor prior to Ramadan did not increase risk of ketonemia, hypoglycemia and dehydration as compared to those patients not on SGLT2 inhibitor. However, careful pre-Ramadan assessment and education including hydration advice is still required for all patients with diabetes who choose to fast [19,20], as Ramadan fast itself is associated with significant changes in weight, BP and eGFR regardless of whether the patient is on SGLT2 inhibitor treatment. It is hoped that these findings will add to the body of knowledge on diabetes management during Ramadan and also provide some guidance to clinicians' decision-making on SGLT2 inhibitor use during Ramadan before evidence-based practical guidelines are made available. Future studies of larger sample size and randomized design assessing various different SGLT2 inhibitors are needed to confirm the safety of SGLT2 inhibitor use during Ramadan fasting.

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Conflict of interest statement

Sum CF has served on advisory board of Janssen, Johnson & Johnson, Singapore. All other authors declare that they have no potential conflict of interest.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diabres.2018.05.022.

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