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ORIGINAL ARTICLE

Safety of sodium-glucose cotransporter 2 inhibitors (SGLT2i) during the month of Ramadan in patients with type 2 diabetes mellitus in Pakistani population—an observational study from a tertiary care center in Karachi

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Abstract

Background and aims Primary aim was to assess the safety of SGLT2-i in patients with Type 2 Diabetes Mellitus (T2D) in a real-life scenario during Ramadan by finding the frequency and severity of hypoglycemic/hyperglycemic events, dehydration, and Diabetic ketoacidosis (DKA). Secondary aim was to assess changes in glycated hemoglobin (HbA1c), weight and creatinine levels.

Methods This prospective, observational, controlled cohort study was conducted at Aga Khan University Hospital, Karachi, Pakistan from March 15 to June 30, 2021. Participants were over 21 years of age, on stable doses of SGLT2-I, which was started at least 2 months before Ramadan. Endpoint assessments were done 1 month before and within 6 weeks after Ramadan.

Results Of 102 participants enrolled, 82 completed the study. Most (52%) were males, with mean age 52.2 ± 9.5 years and average duration of T2D 11.2 ± 6.5 years. 63% were on Empagliflozin (mean dose; 14.8 ± 7.2 mg/day) whereas 37% were on Dapagliflozin (mean dose; 8.2 ± 2.7 mg/day). Six (7.3%) documented symptoms of hypoglycemia. However, no episode of severe hypoglycemia, hyperglycemia, dehydration, DKA, hospitalization or discontinuation of SGLT2i was reported. HbA1c changes were (7.7 ± 1.2% from 7.9 ± 2.3%, p 0.34), weight (78.4 ± 12.9 kgs from 78.9 ± 13.3, p 0.23) and eGFR (87.8 ± 27.9 from 94.3 ± 37.6, $p < 0.001$). The reasons of study participants drop outs were: six did not keep any fasts; four discontinued study participation for personal reasons; three were out of city and missed post Ramadan follow-up, two protocol violation and five could not be contacted for post-Ramadan follow up during the third wave of COVID-19.

Conclusion Results showed the safety of SGLT2i agents during Ramadan in the Pakistani population recommending it as a treatment option in adults with T2D, without any additional adverse events.

Keywords Type 2 diabetes mellitus · Ramadan · Sodium-glucose cotransporter 2 inhibitors (SGLT-i) · Safety

Introduction

Diabetes is a highly prevalent noncommunicable disease that has no cure and needs execution of continuous self-care principles and medical management to prevent acute and chronic complications. In 2021, the global population of diabetics was estimated to be 537 million. With an ever-increasing number of participants in this group, as evidenced by studies, the population with Diabetes is expected to be 738 million by 2045 [1]. Approximately 150 million Muslims worldwide suffer from diabetes, and this figure is also increasing gradually. Evidence suggests that 118 million of these Muslims with Diabetes observe fasts during Ramadan stating the need for the right choice of treatment

The study was presented as poster presentation at IDF 2021 and as oral paper presentation at Pakistan Endocrine Society's annual meeting 2021 and 8th International Diabetes and Ramadan Conference 2022.

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plan during this period [2]. According to CREED and Epidemiology of Diabetes and Ramadan studies, around two-thirds of all Muslims with type 2 diabetes mellitus (T2D) fast during the month of Ramadan [3, 4]. Likewise, the most recent study reported that 86% of the participants with T2D observed a fast for at least 2 weeks [5]. Managing Diabetes during fasting periods is a great challenge for clinicians to design and advocate a plan that ensures healthier food choices, recommends beneficial physical activities, and identifies the right medication and dosages to prevent complications. Whereas an individual is solely responsible for self-care management, the identification of safe and effective medication is the concern of the clinician especially when the patient needs spiritual and health benefits during the Holy month of Ramadan.

Being a Muslim, it is mandatory to fulfill five religious obligations that comprise the five pillars of Islam. Fasting during the month of Ramadan (ninth month of the lunar year) is one of these five pillars that is mandatory for all healthy adult Muslims [2]. Other than the spiritual benefits of being blessed, fasting enables an individual to improve health through self-control. During fasts; a muslim must abstain from food and drink (including medicines), from dawn till sunset. The average duration of this abstinence varies from 12 to 18 h, depending upon the part of the world and the season of the year [6]. Although fasting during Ramadan is reported to have favorable changes in patients with Diabetes such as a decrease in excess body weight and an improvement in lipid profile [7, 8], it can be associated with a slightly increased risk for metabolic complications that require immediate attention such as hypoglycemia and hyperglycemia, dehydration, and Diabetic ketoacidosis (DKA) [4, 8–10]. The use of oral antidiabetic medications during Ramadan, therefore must have sufficient evidence regarding safety and efficacy.

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are the most emergent class of oral antidiabetic medications with cardio and renal benefits [11]. In the literature published so far, SGLT2i has shown lower rates of hypoglycemia and hypovolemia during fasting as compared to sulphonylureas (SU) [12–14]. The data regarding the safety and effectiveness of SGLT2i to address the associated risk for metabolic complications, such as hypoglycemia and hyperglycemia, dehydration and DKA still needs further exploration.

Pakistan is a populous country where a majority of Muslims fast during Ramadan. Since Pakistan ranks third in the prevalence of diabetes, an unmet need regarding the safety and efficacy of the use of SGLT2i during Ramadan is felt.

Thus, we aimed this study to assess the safety of this group of oral antidiabetic agents during Ramadan fasting, in a real-world scenario, in terms of the frequency and severity of hypoglycemia, dehydration and DKA. And also, its effectiveness in terms of the change in weight, glycated hemoglobin (HbA1c) and estimated glomerular filtration rate (eGFR) during the fasting period.

Materials and methods

Study design and setting

This was a prospective, observational, controlled cohort study carried out in the outpatient endocrinology clinics at Aga Khan University Hospital (AKUH), Karachi, Pakistan. Additionally AKUH has laboratory collection points located throughout the city that are fully equipped to conduct clinical and lab assessments. During the COVID wave when mobility was restricted these collection points were used for study follow-up visit for few patients. Study endpoints were assessed within 4 weeks before Ramadan and within 6 weeks after Ramadan.

The endocrinology clinics receive around 160 patients on a daily basis; 90% of these patients have T2D and 97–98% of patients are Muslims. Ethical approval was obtained from the University's Ethics Review committee. Detailed informed consent was obtained from all study participants after explaining the details and importance of the study.

Selection of participants

Participation in the study was offered to T2D patients between the ages of 21 to 70 years who intended to fast during Ramadan, exhibited no contraindication to fasting, the doses of SGLT2i were stable for at least 8 weeks before Ramadan and agreed to monitor their capillary blood glucose at least five times a week, especially at the time of the development of hypoglycemic symptoms. Participants with eGFR <45 ml/min/1.73 m^2 and women who were either pregnant or planning to conceive were excluded from participation. Patients who discontinued the SGLT2i before or during Ramadan and those who fasted for less than 15 days were excluded from the final analysis.

Participants were enrolled within one month before Ramadan in the Islamic year 1442 Hijri, i.e., March, April 2021.

Data collection procedure

A research officer trained for research data collection was posted in the endocrinology clinics, to assess the patients for their eligibility in the study. Patients meeting the selection criteria were approached for their willingness to participate.

Pre-Ramadan assessments

Patients willing to participate were interviewed by the research officer, their medical records were reviewed, and

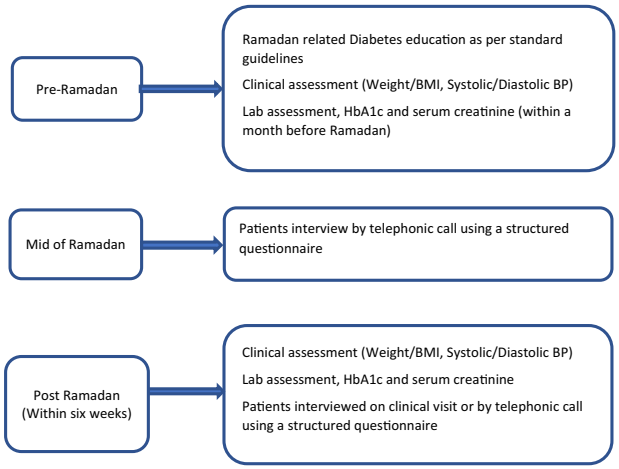

Fig. 1 Data collection procedure

clinical assessment including weight, body mass index (BMI), systolic and diastolic blood pressure was recorded. The dose of SGLT2i was shifted to Iftar time and the SU/Insulin dose was adjusted for Ramadan. Participants were given Ramadan-related Diabetes education as per standard guidelines. During pre-Ramadan assessment, the awareness and recognition of warning symptoms of hypoglycemia were assessed and its management was reinforced. A structured data collection form comprising questions on demographics, clinical characteristics, comorbid conditions, the dose of oral and injectable antidiabetic medications, and the dose of SGLT2i (empagliflozin or dapagliflozin) was developed and all information was recorded. (Fig. 1: Data collection procedure).

Pre-Ramadan lab assessments comprised of HbA1c (performed within one month before Ramadan), and baseline serum creatinine and eGFR. HbA1c was analyzed by immunoassay method on ADVIA 1800 chemistry analyzer (Siemens Diagnostics, NY, US) using manufacturer-provided recommendations; which is a National Glycohemoglobin Standardization Program certified and traceable to the Diabetes Control and Complications Trial (DCCT) reference method.

Serum Creatinine was assayed with the rate-Jaffe reaction on ADVIA 1800 chemistry analyzer, (Siemens Diagnostics, NY, US) using manufacturer-provided recommendations, which is traceable to an isotope dilution mass spectrometry reference method.

Estimation of GFR (eGFR) was done using the Chronic Kidney Disease Epidemiology Collaboration, Pakistan (CKD-EPI Pak) equation [15].

Ramadan assessments

A structured study questionnaire was developed and used to interview the participants through a telephone call during the middle of Ramadan. The questions included the number of days fasted, the number of events of symptomatic and documented hypoglycemia, the timing of hypoglycemia, any complaint of extreme and unusual thirst, any hospitalization to manage hypoglycemia and hyperglycemia, extreme dehydration or DKA.

Post-Ramadan assessments

The same questionnaire was re-administered for the 6 weeks post-Ramadan assessment and responses were recorded. Participants' weight and blood pressure (systolic and diastolic) were recorded. HbA1c, serum creatinine, and eGFR were measured. Since Pakistan was going through the third wave of the COVID-19 pandemic, the questionnaire was administered via telephone to participants who could not visit the main endocrine clinic while clinical and lab assessments were conducted at the laboratory collection points located throughout the city. All information was transcribed onto the data collection sheet.

Confidentiality was maintained and no identifiable information about study participants such as their names, addresses, and contact numbers were noted in the data collection sheet. All the collected data were stored in a password-protected computer.

Statistical analysis

Data analysis was done by using STATA version 14.0. For continuous variables like age and HbA1c, mean ± standard deviation, or median with interquartile range was expressed depending on the normality assumption. Categorical variables like gender, frequency, and percentages were reported. Chi-square test was used to measure the association between two categorical variables, while two independent *t* tests were used to measure the association of continuous variables. A p value of ≤0.05 was considered statistically significant.

Results

A total of 102 patients were enrolled in the study before Ramadan while 82 patients completed the study. The reasons of study participants dropouts were: six did not keep any fasts; four discontinued study participation for personal reasons; three were out of city and missed post Ramadan follow-up, in two there was protocol violation and five could not be contacted for post- Ramadan follow up during the third wave of COVID-19. (Supplementary Fig.: Study flow diagram). The mean age of study participants was 52.2 ± 9.5 years. Out of 82 patients,

Table 1 Baseline characteristics ($n = 82$)

Pre-Ramadan characteristics	Number (%)
Age[a]	52.2 ± 9.5
Sex	
• Male	43 (52.4)
• Female	39 (47.6)
Duration of diabetes (in years)	11.2 ± 6.5
Weight (kg)[a]	78.9 ± 13.3
Serum creatinine (mg/dl)[a]	0.9 ± 0.4
eGFR (mL/min/1.73 m^2)	
• 45–60	12 (14.6)
• >60	70 (85.4)
Systolic BP (mm/Hg)[a]	132.7 ± 15.1
Diastolic BP (mm/Hg)[a]	72.9 ± 10.2
Hypertension	33 (40.2)
Dyslipidemia	35 (42.7)
Coronary artery disease	7 (8.5)
Hypothyroidism	2 (2.4)

[a]Mean ± SD

43 (52.4%) belonged to the male gender (Table 1). The mean duration of T2D was 11.2 ± 6.5 years. The majority of the patients had an eGFR level >60 with a mean serum creatinine level of 0.9 ± 0.4 mg/dl. Forty percent of the patients had hypertension with mean systolic blood pressure (BP) and diastolic BP of 132.7 ± 15.1 and 72.9 ± 10.2, respectively. A total of 35 (42.7%) patients had dyslipidemia, 7 (8.5%) had coronary artery disease and 2 (2.4%) had hypothyroidism.

In addition to SGLT2s (empagliflozin or dapagliflozin) majority of the patients 71 (86.6%) were taking Metformin followed by Gliptin 39 and SUs 24 (Table 2). Around 21% of patients were taking premixed insulin with the mean dose of 51.1 ± 21.4 units/ day, while 19.5% were taking basal insulin.

Patients were assessed on clinical outcomes using a questionnaire. The majority of patients, 92.6% fasted for more than 25 days, out of these 70 (85%) fasted for the entire month. Six (7.3%) patients reported symptomatic hypoglycemia that was subsequently confirmed with the capillary blood glucose test through glucometer. Out of six patients, four (66.6%) reported that the event occurred at midday. (Sub-analysis of these six patients is reported in Supplementary Tables 1 and 2). Four (4.8%) patients reported symptomatic dehydration. There was no hospital admission due to hypoglycemia, hyperglycemia, extreme dehydration, and DKA (Table 3).

Secondary study endpoints including HbA1c, weight, serum creatinine, eGFR, and systolic and diastolic blood pressure were assessed in patients before and after Ramadan (Table 4). There was a significant difference between the pre-Ramadan eGFR and post-Ramadan eGFR with a p value of <0.001.

Table 2 No. of patients taking anti-diabetic medication and their mean dose

Anti-diabetic medications	n (%)	Mean dose ± SD
Empagliflozin	52 (63.4)	14.8 ± 7.2
Dapagliflozin	30 (36.6)	8.2 ± 2.7
Metformin	71 (86.6)	1620.4 ± 483.1
Sulphonylureas	24 (29.3)	53.1 ± 38.0
Gliptin	39 (47.6)	89.4 ± 23.9
Glitazone	8 (9.8)	18.7 ± 6.9
GLP1 agonist	8 (9.8)	1.4 ± 0.4
Premix insulin	17 (20.7)	51.1 ± 21.4
Basal Insulin	16 (19.5)	41.9 ± 46.0
Bolus insulin	5 (6.1)	76.2 ± 66.1
Combined (basal + bolus)	4 (4.9)	90 [63–258]
Metformin and gliptin	37 (45.1)	-
Metformin and Insulin (any)	31 (37.8)	-

Table 3 Primary outcome measures

Primary outcome measures	n (%)
No. of patients with reported symptomatic hypoglycemia	6 (7.3)
No. of reported events of hypoglycemia	6 (7.3)
Timings of hypoglycemia	
• Morning	1 (16.7)
• Midday	4 (66.6)
• Before iftar	1 (16/7)
Days of fasting (mean ± SD)	28.0 ± 3.1
• 15–25 days	6 (7.3)
• 25–29 days	76 (92.6)
Need of hospital admission as a result of hypoglycemia	0 (0.0)
Need of hospital admission as a result of hyperglycemia	0 (0.0)
No. of patients with reported symptomatic dehydration	4 (4.8)
Need of hospital admission as a result of extreme dehydration	0 (0.0)
Need of hospital admission as a result of DKA	0 (0.0)

Table 4 Study endpoints with changes post Ramadan

Variable	Pre-Ramadan	Post-Ramadan	p value
HbA1C (%)[a]	7.9 ± 2.3	7.7 ± 1.2	0.34
Weight (kg)[a]	78.9 ± 13.3	78.4 ± 12.9	0.23
Creatinine (mg/dl)[a]	0.9 ± 0.4	0.9 ± 0.2	0.09
eGFR(mL/min/1.73m^2)[a]	94.3 ± 37.6	87.8 ± 27.9	<0.001
Systolic BP (mm/Hg)[a]	132.7 ± 15.1	138.1 ± 16.9	0.14
Diastolic BP (mm/Hg)[a]	72.9 ± 10.2	73.8 ± 10.0	0.53

[a]Mean and SD

Discussion

Diabetes Mellitus, being a metabolic disease can be greatly impacted by changes in meal timings and sleep patterns observed during Ramadan. The antidiabetic treatments, along with the complications of Diabetes and comorbid conditions, thus make the management of diabetes during Ramadan fasting quite challenging for the treating physicians [16].

SGLT2i is a relatively newer group of anti-diabetic agents that are efficacious with a reasonable safety profile and have shown promising results in terms of cardiac and renal benefits [17–21], hence physicians would want to continue with this group of drugs during Ramadan fasting as well. At the same time because of the diuretic effects and reported cases of diabetic acidosis, dehydration, and volume depletion [22, 23], there are theoretical concerns regarding the safety of SGLT2i during Ramadan fasting especially during summer when fasting hours are long.

In the above context, we assessed the safety and efficacy of this novel oral antidiabetic agent in the Pakistani population during the Ramadan fasting. Similar to other studies conducted on different population cohorts, the results of our study are consistent in terms of the safety and efficacy of SGLT2i during Ramadan fasting [12].

Only six (7.1%) of the study participants reported symptoms of hypoglycemia confirmed by blood glucose measurement. Hypoglycemia was mainly observed in female patients and the timing of its occurrence was midday. The result of hypoglycemia with SGLT2i is in the similar range as reported by Elsayed A Eid et al. [24] (7%) and Wan et al. [14] (6.9%). Four out of six patients with reported hypoglycemia were on premixed insulin and two were on SUs, agents that have the potential to cause hypoglycemia even outside Ramadan fasting. The hypoglycemia was of mild intensity since none of these patients' needed assistance for its management or hospitalization. This lower occurrence of hypoglycemic events in patients with SGLT2is alone or with other combinations can be attributed to their insulin-independent mode of action [25].

Only four (4.8%) study participants reported having symptoms of volume depletion, e.g., postural dizziness or hypotension, or intense thirst. This is lower than studies done previously in almost similar settings, where volume depletion is reported to be between 5.9% [24] and 9.3% [26]. The reason behind this lower frequency could be the better knowledge of healthcare physicians and patients', awareness over time to deal with volume loss caused by SGLT2i, and improved Ramadan education regarding hydration with each passing year.

There was slight improvement noted in the pre- and post-Ramadan HbA1c level (7.7 ± 1.2 from 7.9 ± 2.3) in the study participants, that could be explained by many factors such as; a preexistent better control at the time of enrollment as compared to previous studies; less than 3 months duration between the two measurements and the fact that Ramadan is a time of fasting and feasting in most of the Muslim households, and adherence to medical nutrition plan is not practiced by the majority. Weight change did not achieve significance as has been reported by Hoda Gad and colleagues in their systematic review and meta-analysis [12].

Though the renoprotective effect of SGLT2is has been reported by many studies and trials outside Ramadan settings [19, 27]; whether the SGLT2i adversely impacts renal function during Ramadan was not evident until the study by Bashier, et al. [26] which reported no detrimental consequences on renal functions. Likewise, we did not observe any deleterious effect on renal functions although there is a statistically significant difference in the eGFR between the pre-and post-Ramadan, the mean eGFR did not fall to an extent that will be clinically meaningful. This finding further supports the safety and efficacy of this group of antidiabetic agents during Ramadan and suggests an area of research for the future.

The total duration of fasting ranged from 14 h to 15 h over the entire month of Ramadan and the average temperatures stayed between 95 and 105-degree Fahrenheit (35–40 degree Celsius) {https://weatherspark.com/h/m/106467/2021/5/Historical-Weather-in-May-2021-in-Karachi-Pakistan#Figures-Temperature}. None of our study participants was a heavy laborer to be negatively affected by the duration of fasting hours and difficult weather conditions. It will be interesting to have more research studies on safety of SGLT2i from other regions of the world which have longer duration of fasting, dissimilar weather conditions and with diverse group of study participants.

The strengths of our study include real-world safety and effectiveness of SGLT2is in patients with Diabetes opting to fast during Ramadan and the availability of data in the Pre-Ramadan, middle of Ramadan, and post-Ramadan period, thus limiting recall bias. Our study has some limitations e.g., being conducted in a single center and the lack of a control arm. Few patients dropped out for the post-Ramadan study visit since Pakistan was going through the third wave of the COVID-19 pandemic during that time. Though the results are quite encouraging and comparable with other studies conducted in other parts of the world, the need for some randomized controlled trials is still felt to confidently advocate the safety and efficacy of SGLT2i during Ramadan fasting in our population.

In conclusion, our study results demonstrated that SGLT2i is safe and effective during the month of Ramadan in the Pakistani population. Overall, findings

from this study support the use of SGLT2i as a treatment option during the month of Ramadan in adults with T2D, without any additional adverse events. Our study results are generalizable to similar populations, weather, and fasting duration and should be interpreted in the appropriate clinical context.

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Author contributions All authors contributed to the study conception and design. A.S.: Concept, design, drafting, revised critically, patient management and approval of the final manuscript. Responsible and accountable for the integrity of the work. B.D.: Concept, design, literature search, drafting, revised critically and approval of the final manuscript. S.S.: Interpretation of data, preparation and approval of the final manuscript. N.I.: Concept, design, supervision, patient management and approval of the final manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethics approval This is an observation study and ethical approval was obtained from the Aga Khan University's Ethics Review committee on 17th May 2019 and extension of ethical approval was obtained on 3rd May 2020 and 25th April 2021.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to publish Our manuscript does not contain any individual person's data in any form (including any individual details, images or videos), thus consent for publication was not required.

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