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Safety and tolerability of sodium-glucose co-transporter -2 inhibitors (SGLT-2i) during Ramadan fasting

ABSTRACT

Background. Diabetic management during Ramadan fasting is a significant clinical challenge. Sodium-glucose co-transporter -2 inhibitors (SGLT2i) are a new class of antidiabetic medications known for the low frequency of associated hypoglycaemia. The present study aimed to evaluate the efficacy, safety and tolerability of SGLT2i in diabetic patients practising Ramadan fasting.

Methods. The study included 94 patients. They comprised 51 patients who received metformin and sulfonylureas (SU): glimepiride (1–6 mg/d) or gliclazide MR (60–120 mg/d) and 43 patients who received metformin and SGLT-2 inhibitors: empagliflozin (25 mg), dapagliflozin (10 mg) or canagliflozin (300 mg). The study outcome parameters were frequency of hypoglycaemia episodes, volume depletion episodes, number of days with early fasting break and missed fasting days.

Results. patients of SGLT-2i group experienced significantly fewer symptomatic (9.3% vs 35.3%, P = = 0.003) and documented (7.0% vs 25.5%, P = 0.017) hypoglycaemic episodes compared to those of SU group. However, there were no significant differences between the studied groups regarding the frequency of patients with volume depletion episodes (5.9% vs 16.3%, P = 0.1). Moreover, there were no significant differences between groups regarding the frequency of patients with early fasting break (11.8% vs 9.3%, P = 0.7) or missed fasting (3.9% vs 2.3%, P = 0.66). None of the studied patients discontinued the prescribed medications.

Conclusions. The use of SGLT-2 inhibitors combined with metformin for diabetic patients during Ramadan fasting is effective, safe and well-tolerated with the advantage of reduced hypoglycaemic events. (Clin Diabetol 2021; 10; 5: 386–388)

Key words: SGLT-2 inhibitors, metformin, sulphonylureas, Ramadan fasting, hypoglycaemia

Introduction

Ramadan fasting is one of the five pillars of Islam. It includes 29–30 days, and the daily fasting hours range from 12–16 hours according to the geographical location. Although most patients with acute and chronic diseases including diabetics are usually exempted from fasting, a large proportion of patients choose to fast [1, 2]. The practice of Ramadan fasting poses a substantial clinical challenge for patients and physicians. The wide fluctuations in blood sugar levels can increase the risk of many metabolic complications including hypoglycaemia, hyperglycaemia, dehydration and even diabetic ketoacidosis (DKA) and thrombosis [3]. One meta-analysis, however, argued that Ramadan fasting isn't associated with an increased risk of DKA [4]. To avoid these consequences, a dedicated management strategy for fasting diabetic patients during Ramadan is required [3, 5]. Elements of this strategy entail proper

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patients' education, balanced nutritional management, close monitoring of blood glucose and appropriate selection and dosing of antidiabetic medications [4, 6].

The sole use of sulfonylureas during Ramadan fasting is linked to higher rates of hypoglycaemia. So, its use is not recommended except in selected cases with extreme caution [7]. Alternatives include metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide -1 (GLP-1) receptor agonists, and sodium-glucose co-transporter -2 (SGLT-2) inhibitors [8–10] SGLT-2 inhibitors are a new type of anti-hyperglycaemic agents used in the management of type 2 diabetes mellitus (T2DM). Many trials showed that SGLT-2 inhibitors proved to be effective glycaemic controllers with good tolerance and minimal side effects. The reported rate of hypoglycaemia with SGLT-2 inhibitors are comparable to placebo except when combined with insulin or an insulin secretagogue [11].

Studies conducted in Malaysia, Singapore, and United Arab Emirates supported the use of SGLT-2 inhibitors for type 2 diabetic patients fasting during Ramadan [12]. It's known, however, that practice of Ramadan Fasting is characterized by considerably variable traditions among different Muslim communities. In Egypt, the main meal is mostly consumed directly after sunset while another meal is consumed at midnight. Egyptian food during Ramadan usually contains relatively high proportions of fat and carbohydrates [13]. Therefore, the present study was designed to evaluate the efficacy and safety profile of SGLT2 inhibitors in Egyptian type 2 diabetic patients in comparison to sulfonylureas.

Material and methods

Patients and study design

This is an observational cohort study that was conducted at Delta University outpatient clinics during Ramadan (April 2019–July 2019). The current study enrolled 94 patients with type 2 diabetes of > 3 months duration, their ages ranged from 25–65 years. They comprised 51 patients who received metformin and sulfonylureas: glimepiride (1–6 mg/day) or gliclazide MR (60–120 mg/day) and 43 patients who received metformin and SGLT2i: empagliflozin (25 mg/day), dapagliflozin (10 mg/day) or canagliflozin (300 mg/day).

Inclusion and exclusion criteria

The inclusion criteria were HbA1c 6.5–8.5 g% before Ramadan and eGFR > 60 ml/min. Patients were excluded if they were on insulin or has contraindications for fasting such as severe renal disease, liver diseases, unstable angina, hypoglycaemic unawareness etc., according to IDF diabetes and Ramadan (DAR) guidelines [14].

Clinical and lab workup

All patients were subjected to careful history taking, clinical examination, BMI and blood pressure measurement before and after Ramadan. Before Ramadan, patients were instructed about the appropriate nutritional and therapeutic management of fasting. Frequent blood glucose monitoring by glucometer at different day times according to DAR IDF guidelines [14]. Also, serum HbA1c, kidney function tests (serum creatinine, eGFR, albumin creatinine ratio), liver function tests (serum albumin, bilirubin, AST, ALT and INR) were measured at the start of the study and by the end of the Ramadan fasting.

Primary outcomes

The primary study outcomes were a) hypoglycaemic episodes during Ramadan (assessed by telephone 2–3 times in Ramadan every 10–14 days by self-measurement of the blood glucose several times during the day according to IDF diabetes and Ramadan (DAR) guidelines for blood glucose monitoring during Ramadan [14]. The reported episode included symptomatic episodes (symptoms of dizziness, visual blurring, palpitations, nausea, sweating, confusion, tremor, or intense hunger with or without biochemical confirmation), documented episodes: fasting blood glucose < 70 mg/dl and severe episodes (episodes for which the patient required assistance from another person or that resulted in seizure or loss of consciousness), b) volume depletion episodes (symptoms of hypotension, orthostatic hypotension, postural dizziness, dehydration, syncope, or presyncope) during fasting and c) a number of days that the patient early fasting break or missed days of fasting. Secondary endpoints were changes in body mass index (BMI) and HbA1c after Ramadan.

Ethical issues

The study protocol was approved by the local ethical committee of Delta University and all patients provided signed informed consent before participation (approval code # RP.18.10.2).

Statistical analysis

Results obtained from the present study were presented as number and per cent, mean and standard deviation or median and range as appropriate. Comparison between categorical variables was achieved using chi-square test while numerical variables were compared using student t-test or Mann-Whitney U test. A P-value less than 0.05 was considered statistically significant. All statistical calculations were performed using SPSS 25 (IBM, USA).

Table 1. Comparison between the studied groups regarding basic data

	SU group N = 51	SGLT–2i group N = 43	P–value
Age (years) mean ± SD	49.9 ± 9.3	50.7 ± 8.9	0.7
Male/female n	25/26	21/22	0.99
Duration of diabetes (years) mean ± SD	4.7 ± 2.4	5.1 ± 2.9	0.53
BMI before Ramadan [kg/m^2] mean ± SD	29.7 ± 4.3	30.3 ± 4.2	0.55
HbA1c before Ramadan (%) mean ± SD	7.2 ± 0.5	7.2 ± 0.4	0.5
Anti-diabetic medications n (%)			
Metformin	51 (100.0%)	43 (100.0%)	–
Gliclazide MR	29 (56.9%)	–	–
Glimepiride	22 (43.1%)	–	–
Empagliflozin	–	22 (51.2%)	–
Dapagliflozin	–	19 (44.2%)	–
Canagliflozin	–	2 (4.6%)	–
Hypertension n (%)	17 (33.3%)	18 (41.9%)	0.39
Duration of hypertension (years) median (range)	5.0 (3.0–13.0)	4.5 (1.0–13.0)	0.29
Antihypertensive medications n (%)			
ACEi	8 (15.7%)	8 (18.6%)	0.83
ARBs	3 (5.9%)	6 (14.0%)	
Amlodipine	1 (2.0%)	1 (2.3%)	
ACEI + Amlodipine	3 (5.9%)	2 (4.7%)	
ARBs + Amlodipine	2 (3.9%)	1 (2.3%)	

BMI — body mass index; MR — modified release; ACEi — angiotensin-converting enzyme inhibitors; ARBs — angiotensin II receptor blockers

Results

Basic data of studied patients

The present study included 94 type 2 diabetic patients. They comprised 51 patients in the metformin + sulfonylurea group and 43 patients in the metformin + SGLT-2 inhibitors group. Comparison between the two studied groups regarding the basic data including age, sex, duration of diabetes, BMI, HbA1c before Ramadan, antidiabetic medications, duration of hypertension and antihypertensive medications revealed no statistically significant differences (Table 1).

Outcome parameters

Regarding the outcome parameters, the levels of BMI and HbA1c after Ramadan fasting showed a non-significant difference between the SGLT-2 inhibitors group and SU group (P = 0.66, P = 0.22 respectively). On the other hand, it was found that patients in the SGLT-2 inhibitors group experienced significantly fewer symptomatic (9.3% vs 35.3%, P = 0.003) and documented (7.0% vs 25.5%, P = 0.017) hypoglycaemic episodes in comparison to the SU group. However, there were no significant differences between the studied groups regarding the frequency of patients with volume depletion episodes (5.9% vs 16.3%, P = 0.1). Moreover, there were no significant differences between the studied groups regarding the frequency of patients with early fasting break (11.8% vs 9.3%, P = 0.7) or missed fasting (3.9% vs 2.3%, P = 0.66) (Table 2).

Discussion

Management of diabetes during Ramadan fasting is a challenging and sensitive issue. Indeed, most Muslims with diabetes insist on fasting even if this is against doctors' warnings (5). On the other hand, fasting may be associated with substantial risks — not only for patients — but also for the community. Some daily activities like driving may be hazardous in a patient with high odds of hypoglycaemic episodes [15]. Pursuit of a balanced path between the patients' right to practice fasting and the possible unwanted consequences of this practice is a clinical priority in this population.

In this context, the present study assessed the safety of the newly introduced SGLT-2 inhibitors in the management of fasting diabetic Egyptian patients. The study demonstrated that a combination of metformin with different SGLT-2 inhibitors medications was associated with significantly fewer symptomatic and documented hypoglycaemic episodes as compared to a combination of metformin and sulfonylureas. These results are consistent with previous studies with different designs conducted on other populations. In agreement with these findings, Wan Seman et al. [16], found

Table 2. Comparison between the studied groups regarding outcome parameters

	SU group N = 51	SGLT-2i group N = 43	P-value
BMI after Ramadan [kg/m^2] mean ± SD	30.0 ± 4.0	29.6 ± 4.1	0.62
HbA1c after Ramadan (%) mean ± SD	7.1 ± 0.4	7.0 ± 0.6	0.22
Patients with hypoglycaemic episodes n (%)			
Symptomatic	18 (35.3%)	4 (9.3%)	0.003
Documented	13 (25.5%)	3 (7.0%)	0.017
Severe	–	–	–
Patients with volume depletion episodes n (%)	3 (5.9%)	7 (16.3%)	0.1
Patients with early fasting break n (%)	6 (11.8%)	4 (9.3%)	0.7
Patients with missed fasting days n (%)	2 (3.9%)	1 (2.3%)	0.66

BMI — body mass index; SU — sulphonylureas; SGLT2-inhibitors — sodium glucose transporter-2 inhibitors

that treatment of fasting diabetics with dapagliflozin and metformin was associated with significantly lower odds of symptomatic and documented hypoglycaemia in comparison to sulfonylureas and metformin combination. Similar conclusions were reported by another study that compared the safety profile of canagliflozin and sulphonylurea added to metformin ± dipeptidyl peptidase-4 inhibitor [17].

On the other hand, Shao et al. [12] found that the changes in the fasting blood glucose levels in diabetic patients treated with SGLT-2 inhibitors (canagliflozin, empagliflozin or both) over two weeks after starting Ramadan fasting were comparable to that reported by patients treated with other medications (sulphonylureas and/or metformin and/or DPP4 inhibitors). However, their findings are limited by the fact that the authors didn't report the frequency of the hypoglycaemic episodes in the studied groups during the follow-up period. Noteworthy, clinicians should be cautious about using any medications combinations during Ramadan fasting as not all combinations work the same way. For example, it was reported that adding SGLT-2 inhibitors to insulin was associated with a higher risk of hypoglycaemic events [18]. The infrequent occurrence of hypoglycaemia with SGLT-2 inhibitors is attributed to its insulin-independent mechanism of action [19].

It has been reported that the frequency of volume depletion episodes with SGLT-2 inhibitors ranges from 1.2% to 1.5% [20, 21]. In the current study, the authors found fewer hypovolemic episodes in the SU group compared to the SGLT-2 inhibitor group. However, this difference was not statistically significant which is in harmony with Wan Seman et al. [16]. The mild osmotic diuresis induced by SGLT-2 inhibitors explains the higher frequency of hypovolemic episodes in those patients [22]. The episodes of volume depletion in the current study were few because the blood glucose level was controlled as evidenced by the level of HBA1c, so the patients enter Ramadan fasting in semi euglycemic state as modification drug therapy was started 2 months before Ramadan fasting according to DAR-IDF guidelines [15]. Also, Ramadan in the year of the study was in the spring which is in good weather with average temperature, so no excessive sweating and no volume depletion.

In the present study, no patients had significant adverse effects that lead to discontinuation or modification of the drug dose and both groups were comparable regarding the number of days with early fast-breaking or missed fasting. These findings agree with previous reports [12, 16]. There are some limitations of the current work such as lack of advanced technology for continuous self-monitoring of blood glucose according to DAR-IDF guidelines all-over the day was very hard to obtain from all subjects as it requires about 7 times for reading per day due to low socioeconomic standards of the patients which give use accurate monitoring for blood glucose variability. Also, there is no documentation for volume depletion measurement. Finally, one of the limitations of the current study was the small number of patients in each group and a big number of patients from different Islamic countries with different weather temperatures required for more reliable and accurate results and for better assessment of the volume depletion episodes which are affected by the environmental temperature.

Conclusions

In conclusion, the use of SGLT-2 inhibitors combined with metformin for diabetic patients during Ramadan fasting is effective, safe and well-tolerated with the advantage of reduced hypoglycaemic events.

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Conflicts of interest

The authors declared no conflict of interest.

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