

Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitor drugs: Assessment of safety in Fasting Diabetics

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Abstract

Introduction: Ramadan is a holy month and the majority of Muslims fast in it, without considering background illnesses. SGLT-2 drugs were available for Pakistani patients recently, and this was the first year to fast in their presence.

Objectives: To assess the risk of hypoglycemia in fasting diabetics using SGLT-2 drugs, comparing it with Sulphonylurea (SU) drugs. Also, a change in HbA1c and eGFR was checked. Hence, evidence was collected to recommend their use in fasting Diabetics with safety.

Material and Methods: A total of 5500 patients from three different sites were included. Only 500 fulfilled the criteria of inclusion. Pregnant, lactating, advanced Chronic Kidney Disease (CKD), and those recording hypoglycemia frequently were not included. Ages between 20 to 70 years, HbA1c between 7 to 11, and patients taking SU or SGLT-2 were included.

Conclusion: The eGFR was comparable in both groups post-Ramadan. HbA1c was significantly reduced in the SGLT-2 group. Bitter taste and thirst were common with the SU group. Hypoglycemia was comparable in both groups. We concluded that SGLT-2 drugs were safe during Ramadan, and caused more HbA1c reduction.

Keywords: Safety, Fasting, Hypoglycemia, SU, Sodium-Glucose Co-transporter.

Introduction

Ramadan is a holy month, where the majority of Muslims prefer to fast, despite odds. It included abstinence from eating or drinking from dawn to dusk. Behavior was similar in diabetics, keen to take chances.¹ In recent years, a new group of drugs called SGLT-2 was introduced for diabetic patients, with not much evidence available in fasting. In Pakistan, these medicines were officially launched at the end of the first half of 2018; therefore local evidence was limited for them.²

There were few groups of medicines used by diabetics that did not cause hypoglycemia. SGLT-2 drugs belonged to the same, with a mechanism not promoting change in body insulin, rather increased excretion of glucose from urine, causing water loss along with it. This can be caution in fasting, because of extreme temperatures in Pakistan, especially in summers.³

In previous literature, EPIDIAR study⁴ showed that there was a 7.5% increased risk of hypoglycemia in patients who wanted to fast. It showed the importance of hypoglycemia as the single most important complication of fasting diabetics. In VECTOR study⁵, comparing SU with Dipeptidyl Peptidase-4 (DPP-4) Inhibitors, it was concluded that 41.7% of patients on SU had hypoglycemia.

Shoa Y et al carried out a study on SGLT-2 in Singapore on patients with similar characteristics. They concluded that fasting led to significant blood pressure and weight reduction, but did not increase the risk of ketonemia. It was carried out in a small population of 68 patients. Moreover, it did not check for HbA1c, eGFR, and hypoglycemia details in these patients.⁶

Alaaeldin Bashier et al studied patients on SGLT-2 drugs in different combinations in Dubai, observing for hypoglycemia. Hypoglycemia was frequent when Insulin was combined with SGLT-2. It was less common when basal insulin or any oral agent including SU was combined. The observation was that weight and HbA1c were reduced significantly, but there was no change in renal function or lipid profile. We conducted a different study. Our patients were using oral medicine only. We compared with SU, known to cause hypoglycemia, keeping euglycemic medicine like DPP4 or Metformin common.⁷

W.J. Wan Seman et al compared SU drugs with Dapagliflozin, on 110 patients. They either continued them on SU, or changed them to Dapagliflozin, and observed hypoglycemia and postural hypotension

during Ramadan. More significant hypoglycemia was present in the SU group with no change in postural blood pressure documented. Our study also compared SU and SGLT-2, with a bigger pool. We also checked for a change in HbA1c, eGFR, and Hypoglycemia. The topic was not widely published from this region.⁸

Hence, we aimed to assess hypoglycemia in fasting diabetics using SGLT-2 drugs and compared it with SU, before, during, and after Ramadan. We also checked for a change in HbA1c and eGFR. In this way, we collected evidence to recommend their safe use.

Materials and Methods

Data of 500 patients were selected from three different sites. Total 2500 patients from site one and 1500 each from site two and three were initially assessed, making the total screened patients 5500. After consent, those who were taking medicines for 6 weeks were included.

Medicine was continued as previous from personal resources, with dose adjustment if required. Patients on additional medicine like Metformin, DPP-4, or a combination of them, were continued as such.

Patients were contacted twice during the study period after induction. After consent, initial interaction, and assessment before Ramadan, they were asked questions second and third times during and after Ramadan. HbA1c and creatinine were recorded at the start and the conclusion after 12 weeks. Also, if the patients experienced any problem, they were instructed to contact the calling doctor from the research team.

For checking blood sugar levels, guidelines from IDF were followed, regarding diabetes and Ramadan.⁹ They recommend that every high and very high-risk patient should check up to 6 times a day. It was only intended to follow these instructions in very high and high-risk groups. Moderate and low-risk patients were relaxed. If hypoglycemic episodes were frequent or required assistance, such patients were excluded.

Results

It was an open-labeled, randomized, two arms, the non-inferiority study was conducted over 12 weeks, from 1 April 2019 to 30 June 2019. The response of patients related to the effects of SGLT-2 inhibitors and SU were observed in relation to hypoglycemia before, during, and after Ramadan. The mean age was 50.40 ± 10.75 years. Minimum was 18 years and maximum, 85 years. Total 222 were taking SU, and 279

SGLT-2. The mean age in SU was 50 ± 11 years, minimum 23 and maximum 80 years. The mean age of SGLT-2 was 51 ± 11 years with a minimum of 18 and a maximum of 85 years. The majority were between 30-50 years, followed by more than 50 years. The chi-square value was 1.145 and the p-value 0.564. The proportion of males taking SGLT-2 was greater than the females when compared with the SU group. It was 57.9 females in SU, and 42.1 males (chi-square= 0.469, p-value= 0.493) (Table 1).

The obesity index of patients was quite high with the majority having BMI greater than 30 (chi-square=13.316, p-value=0.004). A large proportion had blood pressure readings within the normal range when included (chi-square=5.483, p-value=0.241). The majority reported that the duration of diabetes was less than five years (chi square=1.309, p-value=0.520). On the assessment of complications, the incidence of dyslipidemia higher in the SGLT-2 than in the SU group (chi square=0.233, p-value=0.629). Nephropathy (chi square=0.044, p-value=0.834) and retinopathy were more in SGLT-2 than SU (chi square=1.236, p-value=0.266). Neuropathy was 24.2% and 34.6%, more in SU group (chi square=4.253, p-value=0.039). Patients on SU had more macro-vascular complications like CVA, CVD, and PVD than SGLT-2 (Table1).

The majority of patients on SGLT-2 had CKD stage 2. Similar trend was noticed in post-Ramadan readings (chi-square=5.900, p-value=0.117). HbA1c of majority of patients before Ramadan was >9 (chi-square=1.635, p-value=0.651) with slightly more in SGLT-2 group. This trend improved after Ramadan. It fell to 7.5-9 range in both groups (chi-square=2.202, p-value=0.332), but more in SGLT-2 group.

Figures 1, 2, and 3 compared the response of patients regarding hypoglycemia before, during, and after Ramadan. Proportion of patients experiencing hypoglycemia before Ramadan in SGLT-2 and SU group was 90.9% and 83.3% respectively (chi-square=6.040, p-value=0.014), but during Ramadan it was only 8.2% and 10.7% (chi-square=0.856, p-value=0.355). After Ramadan incidence decreased further with 6.7% and 7.4% in both groups (chi-square=5.012, p-value=0.082). Patients experiencing symptomatic hypoglycemia before Ramadan (chi-square=6.178, p-value=.046) was almost equal to those experiencing symptoms during Ramadan (chi-square=0.799, p-value=0.372). It indicated that patients were unaware to check BSR level when they experienced hypoglycemia during fast. More patients on SGLT-2 required assistance and/or admission

during event of hypoglycemia (chi-square=0.582, p-value=0.446), but after Ramadan it was greater in the SU group (chi-square=0.528, p-value=0.468), and patient required assistance during Ramadan (chi-square=1.049, p-value=0.592). Patients documenting low BSR without symptoms were equal in both groups before Ramadan and more with SGLT-2 during and after Ramadan. It showed that patients taking SGLT-2 were more aware of treating symptoms of hypoglycemia before and during Ramadan. After Ramadan, 17.8% of patients in the SU and 12.8% in the SGLT-2 were aware of treating low BSR without symptoms. The incidence of feeling more thirst during fast and bitter taste in the mouth was more in the SU as compared to the SGLT-2 group.

Table 1: Comparison Of Basic Characteristics In two Groups

PARAMETERS		SGLT-2	SULFO NYL UREAS	CHI-SQUARE	P-VALUE
AGE	<30	3.9%	1.8%	1.145	0.564
	30-50	73.5%	75.5%		
	>50	25.6%	22.7%		
GENDER	MALE	45.2%	42.1%	0.469	0.493
	FEMALE	54.8%	57.9%		
BMI	UNDERWEIGHT	0.5%	0.0%	13.316	0.004
	NORMAL	16.8%	9.4%		
	OVERWEIGHT	37.4%	29.1%		
	OBESE	45.3%	61.5%		
BLOOD PRESSURE	NORMOTENSIVE	52.1%	46%	5.483	0.241
	PRE-HYPERTENSIVE	18.8%	24.3%		
	STAGE-1 HYPERTENSIVE	12.2%	16.7%		
	STAGE-2 HYPERTENSIVE	11.3%	9.1%		
	STAGE-3 HYPERTENSIVE	5.6%	4%		
	HYPERTENSIVE				
DURATION OF DIABETES	<5	66.7%	72%	1.309	0.520
	5-10	23.4%	17.9%		
	>10	9.9%	10.1%		
DYSLIPIDEMIA	YES	32.9%	30.9%	0.233	0.629
	NO	67.9%	69.1%		
RETINOPATHY	YES	55.7%	50.7%	1.236	0.266
	NO	44.3%	49.3%		
NEUROPATHY	YES	24.2%	32.6%	4.253	0.039
	NO	75.3%	67.4%		
NEPHROPATHY	YES	19.2%	18.4%	0.044	0.834
	NO	80.8%	81.6%		
CVA	YES	1.8%	1.4%	0.131	0.718
	NO	98.2%	98.6%		
CVD	YES	0.9%	1.8%	0.661	0.416
	NO	99.1%	98.2%		
PVD	YES	13.7%	20.6%	4.017	0.045

PRE-RAMAZAN eGFR	NO	86.3%	79.4%	9.541	0.023
	CKD STAGE1	33.9%	48.7%		
	CKD STAGE2	40.2%	37%		
	CKD STAGE3a	24.9%	10.9%		
	CKD STAGE3b	1.8%	3.4%		
	CKD STAGE4	0.0%	0.0%		
POST-RAMAZAN eGFR	CKD STAGE1	36%	47.5%	5.900	0.117
	CKD STAGE2	39.5%	36.4%		
	CKD STAGE3a	21.9%	11.9%		
	CKD STAGE3b	2.6%	4.2%		
	CKD STAGE4	0.0%	0.0%		
	CKD STAGE5	0.0%	0.0%		
PRE-RAMAZAN HbA1c	6.5-7.5	13.6%	15.9%	1.635	0.651
	7.5-9	18.9%	18.2%		
	>9	66.9%	65.9%		
POST-RAMAZAN HbA1c	6.5-7.5	17.2%	16.6%	2.202	0.332
	7.5-9	50.0%	42.4%		
	>9	32.8%	41.1%		

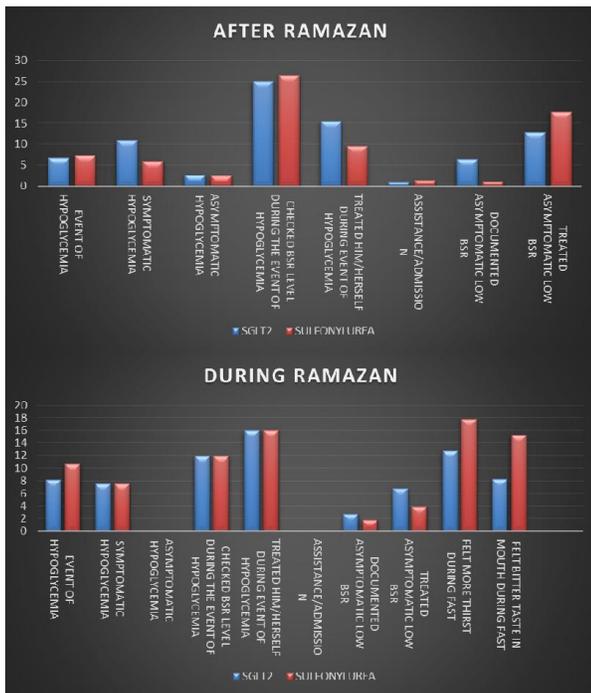


Figure: 1 Comparison of Hypoglycemia during Ramadan

Discussion

Different characteristics in both groups were compared. According to age, the majority were between 30-50 years. The possible reason could be that this age group roams independently, hence the easy approach to the hospital. Our center was a tertiary care center, situated on the first floor. This could be another difficulty for middle-aged and elderly patients.

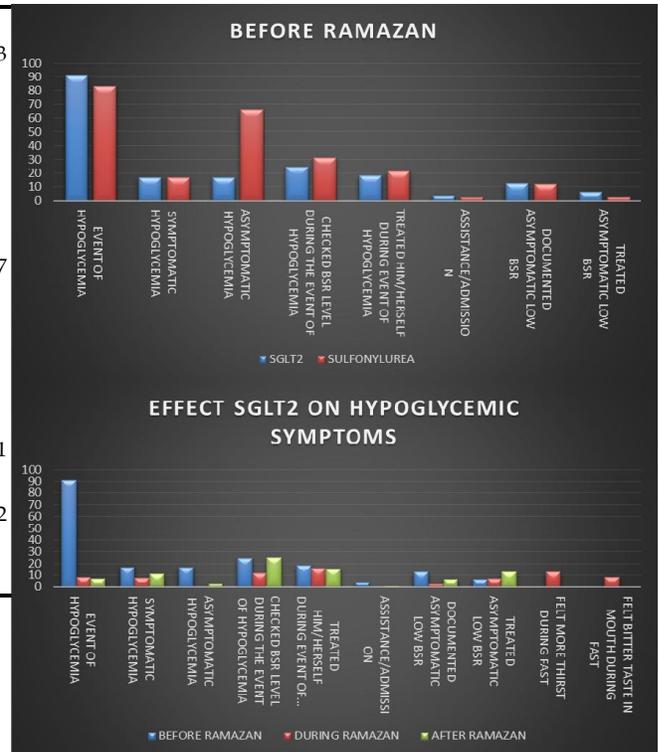


Figure: 2 Comparison of Hypoglycemia before Ramadan

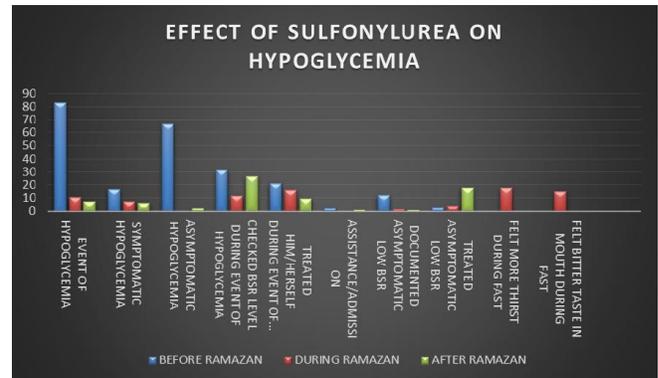


Figure: 3 Comparison of Hypoglycemia of Sulphonylureas Before, During, and After Ramadan

Females were more in attendance. The reason could center timings between 8 to 2 PM, with difficulty for working class. We also know that long waiting hours in the public sector make it difficult for most patients. Benner et al¹⁰ have compared the age difference in their study, with a 10-year group difference. Their findings were different probably due to available resources in Turkey and age difference.

Aydin et al¹¹ carried out a meta-analysis to ascertain the effects of Ramadan fasting on HbA1c, postprandial

glucose, fasting glucose, Body mass index (BMI), and fructosamine levels. They concluded that the use of single or multiple medications in Ramadan did not affect postprandial and fructosamine levels, but it had beneficial effects on BMI, Fasting Glucose, and HbA1c. The majority of overweight patients in our study were on SGLT-2, but the obese category was more in SU (SU). This could be incidental, but one explanation was that intake of SU for a longer period tends to increase weight. Our SGLT-2 patients were overweight or obese. However, we noticed that there were more obese patients in the SU group.

Shao et al¹² have already published that the blood pressure-lowering effect was well known with SGLT-2 drugs during Ramadan fasting. Why our patients showed higher blood pressure in stages 2 and 3 at the time of induction before Ramadan? We cannot justify it. A probable reason could be patient selection bias. On the other hand, why were normotensives more in the SGLT-2 group, we could not explain to satisfaction. It could be just by chance. The majority of our patient's diabetes duration was less than 5 years, suggesting that patients reported here early with the disease. Also, there were a large group of patients on newer drugs like SGLT-2, showing that our healthcare professionals had adequate knowledge on starting a new medicine, and were confident users.

Almalki and Alshahrani¹³ et al have concluded that complications like hypoglycemia, hyperglycemia, and lifestyle change should be addressed to minimize complications. In our study, we found that Dyslipidemia and Nephropathy were equal in the distribution in both groups. Reasons were not known to us. We need more local evidence on this. Retinopathy and Cerebrovascular disease were more in the SGLT-2 group. Similarly, neuropathy, cardiovascular disease, and peripheral vascular disease were more in the SU group. Neuropathy is microvascular and develops early, whereas the other two develop late. Why were these differences between the two groups? An explanation could be just by chance, and we require more local evidence to find out the reason.

Bener et al¹⁰ documented that fasting had a significant beneficial effect on HbA1c reduction, but the effect on creatinine was not statistically significant. When comparing eGFR for pre and Post-Ramadan, we found that except for CKD stage 2 and 3a, the rest of the values were higher in the SU group, with the p-value insignificant. There was decreased in both these stages for SGLT-2 after Ramadan, suggesting no adverse effects of fasting with SGLT-2. We recommend more

studies to support these findings. For the HbA1c comparison of pre and Post-Ramadan groups, there was a significant reduction in the SGLT-2 group having HbA1c more than 9%. The rise was noted in the group between 7.5 and 9%. It suggested that the higher the HbA1c more was positive responses during fasting. However, further studies were needed to validate our findings.

Raveendran and Zargar et al¹⁴ have documented that fasting in diabetics can pose a medical challenge to both patients and health care professionals, and with proper guidance, risks can be reduced. The most important part of our study was to assess the hypoglycemic effects of these medications in comparison, before, during, and after Ramadan. Six questions were asked in all three periods. First, whether they experienced any hypoglycemic symptoms? Second, did they note blood sugar levels at that time, and what was it? Third and fourth, if they were able to self-treat or required assistance. Fifth, if they had asymptomatic hypoglycemia, and finally, if they felt and treated hypoglycemia without checking.

Mansouri et al¹⁵ carried out a study on self-monitoring of blood sugar during Ramadan. They concluded that sugar levels fluctuated with age, and with better understanding and change in lifestyle, fasting can be made safe. In our study, hypoglycemia was higher in the SGLT-2 group before Ramadan, which decreased significantly during and after, as compared to the SU group. We cannot justify the reason, but maybe due to discipline during Ramadan, conscious about hypoglycemia with a new drug, and checking it more frequently.

Aldawi et al¹⁶ carried out a study, comparing glucose excursions during fasting with Continuous Glucose Monitoring (CGM) device. They concluded that there was not much difference before, during, or after Ramadan when using oral drugs, except Insulin and SU drugs. In our study regarding checking blood sugar levels when symptomatic hypoglycemia, it was noted that the SU group had more frequency before Ramadan in all three periods and kept on decreasing. The reason could be dose change, diet composition, discipline about diet, and intake of high caloric food with delayed-release during Ramadan. We need more studies on the composition of a diet to support our justification.

Lee et al¹⁷ compared two groups for hypoglycemia, using telemedicine monitored sugar levels with a control group. They documented significantly better results for the telemedicine group in symptoms and HbA1c at completion. In our study self-treatment of

hypoglycemia, SU group was more frequent before, with a decrease seen during, and significant fall in post-Ramadan period. However, the frequency was higher in the SGLT-2 group Post-Ramadan. The reason could be that patients were more conscious about hypoglycemia during Ramadan and were confident in the Post-Ramadan period regarding managing their diabetes, resulting in better responses. However, we could not explain why the SGLT-2 group had a higher frequency in the Post-Ramadan period. A probable reason could be the careless attitude of patients in this group regarding intake of diet. We need more studies to find out the exact levels which were treated as hypoglycemia.

Hassanein et al¹⁸ compared two different insulins for safety in Ramadan. They concluded that less hypoglycemia and/or assistance was required when new insulin degludec/insulin aspart (IDegAsp) was used. We had used oral medicines for safety comparison. Regarding assistance for hypoglycemia, the SGLT-2 group required more assistance before Ramadan. Being a euglycemic medicine, it was not expected, and the possible reason could be anything from lifestyle to concomitant medicine intake. There was no difference between the two groups during Ramadan. Post-Ramadan minor difference was more frequent in the SU group, which was already anticipated.

Badshah et al¹⁹ reviewed multiple articles and documented that hypoglycemia was a very challenging complication in Ramadan. In our study, we found that asymptomatic patients could also have hypoglycemia. The frequency was higher in the SGLT-2 group in the Pre-Ramadan period. It decreased during and Post-Ramadan period, but still higher in the SGLT-2 group. Our expectation was otherwise. SU group was more likely to cause hypoglycemia. Justification could lie in the half-life of SGLT-2 drugs, long duration of fast and possible changes in lifestyle, which were not checked here. We, therefore, suggest more randomized trials.

Elhadd et al²⁰ studied fasting diabetics using multiple drugs. They found more hypoglycemic episodes with increasing medicine and suggested simpler regimens for Ramadan. We found that symptomatic non-documented hypoglycemia patients were quite a few. SGLT-2 group had more frequency in pre and during Ramadan period, but Post-Ramadan it was higher in SU group. It was expected that SU group patients were more likely to suffer from symptomatic hypoglycemia than the SGLT-2 group, but why was it different before and during Ramadan? The reason could be in

the frequency of monitoring and confidence of patients. More studies were needed to assess this behavior.

Mudher Mikhael et al³ studied the safety of new drugs in Ramadan, documenting increased thirst sensation as a side effect of SGLT-2 drugs. Since SGLT-2 drugs were known to lose water from the body, we checked if they caused thirst and bitter taste, and found that both symptoms were more with the SU group. The bitter taste can be explained, but why increased thirst with SU? A possible reason could be poor glycemic control, leading to increased urine frequency. Since we have not documented urine frequency, we would recommend more trials to prove it.

Conclusion

The majority of our patients attending clinics were between 30-50 years of age, with predominant females. Most of the patients also had a duration of fewer than 5 years, and patients of obesity and overweight were comparable in both groups. Micro and macrovascular complications were present on both sides. CKD stage 2 and 3a were present more with the SGLT-2 group and showed improvement during and after Ramadan, suggesting it was safe during fast. HbA1c was higher at the start in both the groups and improved more significantly in the SGLT-2 group. Bitter taste and thirst were more common with the SU group. Hypoglycemia was comparable in both groups. We concluded that SGLT-2 drugs were safe for fasting diabetics, and caused more HbA1c reduction.

Limitations

First, both groups were not matched completely. The numbers of patients were also different. Results could be different if it was taken care off. Second, we did not record the number of days fasted by the individual but was inquired if they had a total of 20 days or more fasting. It was therefore not mentioned in the methodology. Third, all study period was majority carried out on telephone questions, with only 2 visits at the induction and conclusion. We may find it different if patients were physically present at the time of each questionnaire.

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