

Safety and Tolerability of Sodium Glucose Co-Transporters-2 Inhibitors Among Elderly Patients with Type 2 Diabetes Fasting Ramadan

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ABSTRACT

Background: One of the main five pillars of Islam is Ramadan fasting and it may carry some hazards on some patients especially elderly patients. Sodium Glucose Co-Transporter-2 inhibitors (SGLT2i) is a new family which introduced in the market few years ago and used to treat patients with Type 2 Diabetes (T2D).

Objective: The objective of this study is to investigate the safety and tolerability of SGLT2i among elderly patients with T2D fasting Ramadan.

Patients and methods: The current study was conducted on 100 patients aged 60 years and more, both males and females (Group 1: 50 patients on vildagliptin and metformin and Group 2: 50 patients on empagliflozin and metformin). Glycated haemoglobin (HbA1c) and estimated glomerular filtration rate (eGFR) were measured before and 2 months after Ramadan. Episodes suggesting hypoglycemia and/or volume depletion were estimated. Days to break fasting were also compared.

Results: The mean age among group 1 was 65.34 + 2.9 years versus 66 + 3.4 years among group 2 [P value: 0.25]. Mean HbA1c before Ramadan was 7.26±0.46 among group 1 versus 7.28±0.53 among group 2 [P value: 0.84]. No statistically significant difference was found regarding episodes suggesting hypoglycemia and/or volume depletion nor days to break fasting.

Conclusion: The conducted study has addressed that SGLT2i may be used safely and well tolerated among elderly patients with T2D fasting Ramadan if patients were well prepared and educated before Ramadan.

Keywords: Elderly, Type 2 Diabetes, Ramadan Fasting, SGLT2 inhibitors.

INTRODUCTION

Ramadan is a holy month for Muslims and its fasting is considered as one of the main five pillars of Islam. Often, Muslims fast 29 to 30 days from the sohor (dawn) to iftar (sunset). Last few years; Muslims in Egypt fasted for a duration ranging from 12 to 16 hours. Although many elderly patients with diabetes have the permission not to fast, but most of them reject this and insist on fasting [1]. On the other hand, Ramadan fasting may carry some hazards on few patients with diabetes especially elderly patients. First of these hazards is fluctuation of blood glucose level that may occur during fasting (hypoglycaemia and/or hyperglycaemia), increased risk of thromboembolic manifestation and increase the risk of ketosis [2].

In addition, Egypt is listed as one of the top ten countries having large number of people living with diabetes. According to the International Diabetes Federation (IDF), 10.9 million people living in Egypt have diabetes (in the age range from 20-79 years) in 2021 and it is supposed to be doubled in 2045 by reaching about 20 million patients with diabetes [3]. Also, in the last few years it was noticed that there is increase in the relative and absolute number of elderlies in Egypt. Central Agency for Public Mobilization and Statistics reported that elderlies represented about 7% of total Egyptian population in 2019 and expected to represent about 12% to the total population by the year 2030 [4].

Prevalence of diabetes is increased with age, subsequently total number of elderly patients having type 2 diabetes (T2D) and willing to fast Ramadan will be increased. Complications of fasting are relatively

higher among elderly in comparison to those younger patients [2].

Sodium Glucose Co-Transporter-2 Inhibitors (SGLT2i) are new family of oral antidiabetic drugs approved to treat T2D, they are recently introduced in the Egyptian market few years ago. They act by inhibition of Sodium Glucose Co-Transporter -2 (SGLT2) receptors in the proximal convoluted tubules, leading to glucosuria and subsequently lowering of the renal threshold of glucose reabsorption by about 50-60 % [5]. Furthermore, this family passed a long journey from neutrality to benefits. Adding to its control of blood glucose, a lot of -well conducted- mega trials have shown that they have more advantages beyond the glycaemic control like decreasing Major Adverse Cardiovascular Events (MACE) and progression of Diabetic Kidney Diseases (DKD) [6].

At the beginning of launching these drugs, there was some worry from diabetologists regarding this family to be prescribed among elderly population with T2D especially those aged above 70 years due to risk of hypovolemia especially during Ramadan fasting. Some trials were conducted to investigate the safety and tolerability of SGLT2i during Ramadan among general population with T2D like Canagliflozin in Ramadan Tolerance Observational Study (CRATOS) trial [7], which concluded that canagliflozin -which is one of SGLT2i- could be used during Ramadan fasting. Nevertheless, some increased risk of hypovolemia during fasting was noticed. We previously studied the use of SGLT2i among Egyptian patients with T2D and we concluded that SGLT2i are effective, safe and well-

tolerated drugs with the advantage of low hypoglycaemic events [8].

To the best of our knowledge, there was no trial conducted in Egypt to investigate the safety and tolerability of SGLT2i among elderly patients with T2D fasting Ramadan specifically.

The objective of this study is to investigate the safety and tolerability of SGLT2i among elderly patients with T2D fasting Ramadan.

PATIENTS AND METHODS

This clinical trial was carried out on 100 Egyptian elderly patients attending geriatric and diabetes outpatient clinics of Specialized Medical Hospital, Mansoura University and private clinics in the period of Ramadan 2022 (1443 year of Hijra). We included both males and females aged 60 years or older after agreeing to participate in the study and their random blood glucose was less than 250 mg/dl and Glycated Haemoglobin (HbA1c) < 8% and already the treatment was well established and tolerated 4 weeks at least before Ramadan.

Exclusion criteria were patients with recently discovered T2D; last 3 months before Ramadan, other types of diabetes rather than T2D, patients with severely uncontrolled diabetes (HbA1c > 8 gm % and/or random blood glucose more than 300 mg/dl).

Also, patients with metformin intolerance were excluded. Moreover, patients who shouldn't fast according to Diabetes and Ramadan (DAR) recommendations [9] were excluded [like decompensated liver cirrhosis, estimated Glomerular Filtration Rate (eGFR) less than 30 ml/min and hospitalization due to hyperglycemic crisis like diabetic ketoacidosis or hyperglycemic hyperosmolar crisis in last year].

Thorough history was taken including history and experience of previous Ramadan fasting. Careful Examination was done for all participants including body mass index (BMI) one month before Ramadan and two months after Ramadan. HbA1c and creatinine were measured before Ramadan fasting and two months after Ramadan, eGFR was calculated using the original Modification of Diet in Renal Disease (MDRD) 4 variable equation.

Patients were divided into 2 groups: **group 1** included 50 patients were taking metformin and vildagliptin (1000/50 twice daily and dose was modified according to eGFR) plus standard of care. **Group 2** included 50 patients were taking metformin 1000 mg twice daily and empagliflozin 10 mg once daily (and dose of metformin was modified according to eGFR) plus standard of care.

The following were assessed: Five self-monitoring of blood glucose (SMBG) reading (2 hours

after sohor, 12 pm, 3 pm, 1 hour before iftar, 2 hours after iftar) at least in the first week of Ramadan fasting or when sense of any symptoms of hypoglycemia or hyperglycemia at any time of the month. Also, Number of episodes suggesting hypoglycemia (like dizziness, visual blurring, palpitations, nausea, sweating, confusion, tremor, or intense hunger with or without biochemical confirmation) was addressed. Documented hypoglycemia was defined as random blood sugar less than 70 mg/dl at any time of fasting.

Moreover, number of episodes suggesting volume depletion (symptoms of hypotension, orthostatic hypotension, postural dizziness, dehydration, syncope, or presyncope) and number of days the patient broke fasting were reported. Patients were educated to break fasting immediately if blood glucose less than 70 mg/dl or more than 300 mg /dl at any time of fasting. Finally, changes of weight, eGFR and HbA1c were measured before and two months after Ramadan. It is to be noted that patients were assessed clinically one month before Ramadan, telephoned every 10 days during Ramadan to assure safety of fasting and re-assessed clinically again two months after Ramadan.

Ethical consent:

Mansoura University's Institutional Review Board approved the study if all participants signed informed consent forms and submitted them to Mansoura University by the code (R.22.04.1672). We adhered to the Helsinki Declaration, the ethical guideline of the World Health Organization for human trials.

Statistical analysis

Data were fed to the computer and analysed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non-parametric data and mean \pm standard deviation (SD) for parametric data after testing normality using Kolmogorov-Smirnov test. Significance of the obtained results was judged at the (0.05) level. Chi-Square test or Fisher exact test for comparison of 2 or more groups for categorical variables. Student t-test or Mann-Whitney U test was used to compare 2 independent groups for parametric and non-parametric data. Paired t test was used to compare between before and after treatment results.

RESULTS

Table (1) shows that there was no statistically significant difference between the 2 groups regarding sociodemographic data nor mean duration of diabetes.

Table (1): Sociodemographic characteristics of the studied groups

	Group 1 (Vildagliptin/metformin) n=50	Group 2 (Empagliflozin/metformin) n=50	Test of significance
Age (Years) (Mean ± SD)	65.34±2.90	66.08±3.49	t=1.15 p=0.252
Sex			
-Males (%)	25 (50 %)	23 (46%)	$\chi^2=0.160$ p=0.689
-Females (%)	25 (50 %)	27 (54 %)	
Special habits			
-Non-smoker	41 (82 %)	41 (82 %)	$\chi^2=0.900$ p=0.638
-Ex-smoker	6 (12 %)	4 (8 %)	
-Current smoker	3 (6 %)	5 (10 %)	
T2D duration (years) Median (min-max)	5 (1-10)	5(1-15)	Z=0.692 P=0.489

t: Student t test, χ^2 : Chi-Square test, Z; Mann-Whitney U test

Table (2) shows that there was no statistically significant difference between the 2 groups regarding HbA1c before and after Ramadan. However, HbA1c was significantly improved in both groups after Ramadan.

Table (2): Comparison of HbA1C level between studied groups before and after Ramadan

	Group 1 (Vildagliptin/metformin) n=50	Group 2 (Empagliflozin/metformin) n=50	Test of significance
HBA1c before Ramadan (%)	7.26±0.46	7.28±0.53	t=0.202 p=0.840
HBA1c 2 months after Ramadan (%)	7.12±0.38	7.09±0.65	t=0.299 p=0.765
Paired t test	t=3.04 p=0.004*	t=2.82 p=0.007*	

Table (3) shows that there was no statistically significant difference between the 2 groups regarding changes in BMI before and after Ramadan. However, BMI was significantly changed in both groups after Ramadan and among empagliflozin group the BMI was decreased and on the other hand BMI was increased among vildagliptin group.

Table (3): Comparison of BMI between studied groups before and after Ramadan

	Group 1 (Vildagliptin/metformin) n=50	Group 2 (Empagliflozin/metformin) n=50	Test of significance
BMI before Ramadan (kg/m ²)	29.76 ± 4.32	30.09 ± 4.28	t=0.389 p=0.698
BMI 2 months After Ramadan (kg/m ²)	30.0 ± 3.99	29.52 ± 4.18	t=0.582 p=0.562
Paired t test	t=2.08 p=0.043*	t=4.38 p<0.001*	

Table (4) shows that there was no statistically significant difference between the 2 groups regarding changes in eGFR before and after Ramadan. However, it is noted that among empagliflozin group there was statistically significant decrease in eGFR after Ramadan.

Table (4): Comparison of eGFR between studied groups before and after Ramadan

	Group 1 (Vildagliptin/metformin) n=50	Group 2 (Empagliflozin/metformin) n=50	Test of significance
eGFR before Ramadan (ml/min)	79.30 ± 9.19	77.96 ± 10.35	t=0.684 p=0.495
eGFR 2 months after Ramadan (ml/min)	78.68 ± 9.96	77.10 ± 10.57	t=0.769 p=0.444
Paired t test	t=1.90 p=0.063	t=2.54 p=0.014*	

Table (5) shows that there was no statistically significant difference between the two groups regarding different episode or day of breaking fasting.

Table (5): Comparison between studied groups regarding numbers of symptomatic hypoglycemia, documented hypoglycemia, symptoms suggesting volume depletion and number of days of breaking fasting during Ramadan

	Group 1 (Vildagliptin/metformin) n=50	Group 2 (Empagliflozin/metformin) n=50	Test of significance
(A) Number of symptomatic hypoglycemia during fasting			
- Number of patients reported no episode of hypoglycemia	42(84.0)	46(92.0)	FET p=0.538
- Number of patients reported one episode	4(8.0)	1(2.0)	
- Number of patients reported 2 episodes	3(6.0)	2(4.0)	
- Number of patients reported 3 or more episode	1(2.0)	1(2.0)	
(B) Number of patients who reported Documented hypoglycemia	5 (10.0)	3 (6.0)	FET p=0.715
(C) Volume depletion			
- Number of patients reported no episode suggesting volume depletion	47 (94 %)	46 (92 %)	FET p=0.637
- Number of patients reported one episode	2 (4 %)	1 (2%)	
- Number of patients reported 2 episodes	1 (2 %)	2 (4 %)	
- Number of patients reported 3 or more episode	0 (0%)	1 (2 %)	
(4) Days of breaking fast	3 (6 %)	2 (4 %)	FET P=1.0

FET: Fisher exact test

DISCUSSION

Elderly patients with T2D who are willing to fast were considered previously as high-risk group for fasting especially with old generation insulins and sulfonylurea. Although many elderly have the chance not to fast, but majority of them are enjoying Ramadan fasting. Nowadays with newer anti-diabetic medications, risk stratification of elderly people with T2D is not based on age only rather than associated comorbidities and socioeconomic status [9].

SGLT2i are new oral antidiabetic drugs approved to treat T2D. They work in an insulin-independent manner and they may carry the risk of hemodynamic changes especially with beginning of their use. In our study 100 elderly patients were included with mean age about 65.34 ± 2.90 years and 66.08 ± 3.49 years among group 1 and group 2 respectively. The mean duration of diabetes among patients was about 5 years. On the other hand, the mean HbA1c before Ramadan fasting among the patients was 7.2%. We telephoned all participants every 10 days to answer their questions and give them instructions to ensure safe fasting as this is noticed to be extremely beneficial in passing Ramadan fasting without any hazards. Unfortunately, there is a paucity of research data and trials that investigate Ramadan fasting among elderly, this makes providing specific recommendations is hard. DAR guidelines recommend careful evaluation for elderly patients with T2D who are willing to fast Ramadan [10].

Previously, we conducted a trial to explore the safety and tolerability of SGLT2i during Ramadan fasting [8], but the mean age among SGLT2i group was 50.7 ± 8.9 years and the control arm was against sulfonylurea. In the current study, our mean age was higher and we compared it to vildagliptin, which is a member of Di-Peptidyl Peptidase-4 inhibitors (DPP-4i). DPP-4i act by stimulating insulin and inhibiting glucagon -in a glucose dependent manner- with minimal hypoglycemic episodes and they have no hemodynamic changes like SGLT2i and also, they are weight neutral [11]. DPP-4i are considered by DAR guidelines as a suitable option for patients with T2D fasting Ramadan especially elderly group [9].

CRATOS trial is multicentre, open-label, observational study conducted on 379 patients with T2D in the Middle East during Ramadan 2016. Investigators of some countries reported 15 hours fasting each day and temperatures reached up to $45-50^{\circ}\text{C}$ in some places like Kuwait and the United Arabs of Emirates [7].

A lot of similarity were noticed between CRATOS study [7] and our study. Mean HbA1c was 7.3 gm %, mean BMI was 30.7 kg/m^2 and mean duration of diabetes was 6.5 years. On the other hand, there was some differences between our study and CRATOS study. The mean age among CRATOS study was 52.3y. Moreover, the mean GFR was 89.9 ml/min (versus 77.9 ml/min in our study), this may be attributed to the

difference between mean age of the two studies and method of eGFR calculation. On the other hand, in our study we have used homogenous group, they were taking only metformin plus empagliflozin versus vildagliptin. In contrast, in CRATOS trial they used different types of oral antidiabetic drugs (including metformin, sulfonylurea and different DPP-4i like sitagliptin, vildagliptin, saxagliptin and linagliptin). After adjustment for confounding factors like (age, gender, BMI, duration of diabetes, baseline investigations ...etc), 26 patients (16%) of patients treated with canagliflozin reported one or more episodes suggesting volume depletion. In the current study only 6% reported similar episodes, this may be attributed to the difference between climate in other countries like Gulf countries, which have higher temperature than Egypt.

Moreover, most of our participants in the study were retired or housewives unlike the CRATOS participants, who were younger and go to their work during fasting period. The current study has also addressed that only 8% of patients in empagliflozin group reported one or more episodes of symptomatic hypoglycemia and this also agree with CRATOS study which mentioned that about 4% of patients on canagliflozin group reported one or more attack of symptomatic hypoglycemia.

Also, **Shao et al.** [12] have conducted a prospective, observational controlled cohort study in Singapore in 2018 on 68 patients with T2D fasting Ramadan using dapagliflozin and canagliflozin with or without additional medication (other oral antidiabetic drugs and/or insulin). They concluded that there were no statistically significant differences seen among SGLT2i groups in comparison to non-SGLT2i group. Also, no cases of severe hypoglycemia were reported.

Finally, regarding use of the SGLT2i in Ramadan, the DAR guidelines recommend initiating SGLT2i at least 2-4 weeks before Ramadan. Furthermore, those who are already using it, its recommended to take it with iftar meal and to drink plenty of water in non-fasting hours. In elderly, it recommended to use SGLT2i after review from specialist and to consider that benefit must exceed the risks of adverse events especially in elderly with impaired GFR or those treated with using diuretics [9].

CONCLUSION

This study has concluded that among elderly patients fasting Ramadan (if well-educated and well controlled before Ramadan), no apparent increase in adverse side effects among patients using SGLT2i..

Financial support and sponsorship: Nil.

Conflict of interest: Nil.

REFERENCES

1. **Ahmed M, Husain N, Elmadhoun W *et al.* (2017):** Diabetes and Ramadan: A concise and practical update. *J Family Med Prim Care*, 6(1):11-18.
2. **Sadikot S, Jothydev K, Zargar A *et al.* (2017):** Clinical practice points for diabetes management during RAMADAN fast. *Diabetes Metab Syndr.*, 11(2): 811-819.
3. **IDF Diabetes Atlas 10th (2021):** The 10th edition confirms that diabetes is one of the fastest growing global health emergencies of the 21st century. Pp. 1-141. <http://www.indiaenvironmentportal.org.in/files/file/diabetes%20atlas%202021>.
4. **Egypt Human Development Report (2021):** Development, a right for all: Egypt's pathways and prospects. https://mcit.gov.eg/upcont/Documents/Reports%20and%20Documents_2092021000_EN_Egypt_Human_Development_Report_2021.pdf
5. **Wright E (2021):** SGLT2 Inhibitors: Physiology and pharmacology. doi: <https://doi.org/10.34067/KID.0002772021>.
6. **Kolesnik E, Scherr D, Rohrer U *et al.* (2022):** SGLT2 Inhibitors and their antiarrhythmic properties. <https://doi.org/10.3390/ijms23031678>.
7. **Hassanein M, Echtay A, Hassoun A *et al.* (2017):** Tolerability of canagliflozin in patients with type 2 diabetes mellitus fasting during Ramadan: Results of the Canagliflozin in Ramadan Tolerance Observational Study (CRATOS). *Int J Clin Pract.*, 71:e12991. <https://doi.org/10.1111/ijcp.12991>.
8. **Eid E, Hussein A, Ghazi H (2021):** Safety and tolerability of sodium-glucose co-transporter -2 inhibitors (SGLT-2i) during Ramadan fasting. *Clinical Diabetology*, 10 (5): 389-393.
9. **Hassanein M, Afandi B, Ahmedani M *et al.* (2022):** Diabetes and Ramadan: Practical guidelines 2021. *Diabetes Res Clin Pract.*, 185:109185. doi: 10.1016/j.diabres.2021.109185.
10. **Hassanein M, Al-Arouj M, Hamdy O *et al.* (2017):** Diabetes and Ramadan: practical guidelines. *Diabetes Res Clin Pract.*, 126:303-316.
11. **Foley J, Jordan J (2010):** Weight neutrality with the DPP-4 inhibitor, vildagliptin: Mechanistic basis and clinical experience. *Vascular Health and Risk Management*, 6: 541-548.
12. **Shao Y, Lim G, Chua C *et al.* (2018):** 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. *Diabetes Research and Clinical Practice*, 142: 85-91.