Original Article

Exploring the Relationship Between SGLT2 Inhibitors and Glycosuria: A Cross-Sectional Analysis

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ABSTRACT

Objective: In order to explore how type and dose of the SGLT2 inhibitors affects the level of urine sugar in type 2 diabetes mellitus patients.

Study Design: Cross-sectional Study

Place and Duration of Study: This study was conducted at the Department of Medicine Khyber Girls Medical College Peshawar from Jan 2023 to Dec 2023.

Methods: A cross-sectional Study was used on 100 patients diagnosed with type 2 diabetic mellitus. Patients were on SGLT2 inhibitors for at least 6 months before they were seen by their GP and offered glycaemic monitoring. Urine glucose was also estimated, and correlation with SGLT2 inhibitor dosage and clinical data were then compared. Descriptive analysis in the form of mean and standard deviation and inferential analysis through p value have been used using SPSS software.

Results: The Mean quantity of glucose in urine was 45 ± 8 g/day. As compared with patients on low doses of SGLT2 inhibitors, the proportion of patients with increased glycosuria was significantly ($p < 0.01$) higher in patients on high doses of the latter. Standard deviation for glycosuria over the study population was 7.5 g/day with an average age of patients 54 ± 6.8 years. Elevated amounts of glucose in the urine were also positively associated with the daily dose of the SGLT2 inhibitor in stable conditions: the correlation coefficient was 0.80 ($p < 0.001$) for patients with baseline glucose levels above 180 mg/dL

Conclusion: SGLT2 inhibitors have also been seen to increase glycosuria in patients being candesartan for type 2 diabetes with this being enhanced by higher doses was found. The results offer evidence for their role in improving glycemic management and reducing hyperglycemia, offering guidance on dose optimization in clinical settings.

Key Words: SGLT2 inhibitors, glycosuria, diabetes, glucose excretion.

Citation of article: Haq A, Khattak IQ, Shah M, Khan H, Irfan M, Shah A. Exploring the Relationship Between SGLT2 Inhibitors and Glycosuria: A Cross-Sectional Analysis. Med Forum 2024;35(8):63-66. doi:10.60110/medforum.350814.

INTRODUCTION

SGLT2 inhibitors have been a major development in T2DM management especially for those with inadequate glycemic control. These inhibitors work through the SGLT2 protein in renal proximal tubule responsible for reabsorption of about 90% of filtered glucose back into circulation. SGLT2 inhibitors reduce plasma glucose concentration by enhancing glycosuria-the elimination of glucose in urine—due to the blockade of SGLT2 transporter in the proximal renal tubolus[1,2]. SGLT2 inhibitors cause glycosuria that has many beneficial effects as described below. It causes caloric loss can lead to weight loss and reduced blood pressure due to osmotic diuresis as a result of increased urinary glucose excretion[3]. In addition to antihyperglycemic action, SGLT2 inhibitors seem to have cardiovascular and renal benefits including the reduction of major adverse cardiovascular events and the slowing of the progression of kidney disease[4], 5o3i. Because of these numerous advantages, SGLT2 inhibitors have been incorporated early in clinical practice especially in patients at risk of cardiovascular and renal events[6].Another important facet of SGLT2 inhibitors unleashing is that glycosuria is related directly with dose and efficacy of the drug. The measurement of glucose in urine is useful index for determining activity of the drug but it can change in response to several factors, for example, initial concentration of glucose at blood, kidney dysfunction, and personal tolerance of the drug[7]. Therefore, glycosuria could provide information into the

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Received: January, 2024
Accepted: April, 2024
Printed: August, 2024

therapeutic effectiveness of SGLT2 inhibitors and provide direction in the management of T2DM[8].As the knowledge of SGLT2 inhibitors increases, the quantity of glycosuria and the clinical outcome of SGLT2 inhibitor treatment has not been investigated sharply. Namely, there is ambiguity to whether increased AM levels are more thoroughly beneficial in glycemic control or whether patients' characteristics, including renal function impairment and concomitant diseases, act as moderators[9,10]. Knowledge about these dynamics is essential when it comes to interaction to treatment that is optimized for the therapeutic outcomes and zeroed on adverse effects. This needs to understand the degree of glycosuria associated with SGLT2 inhibitor therapy in patients with T2DM and the extent to which urinary glucose excretion and glycemic control vary with SGLT2 inhibitor dose. Thus, the analysis of these relationships in a clinical context of a real-world setting will contribute to the understanding of possibilities to apply SGLT2 inhibitors in clinical practice, including adjustment of the drug dose and evaluation of therapeutic outcomes[11,12].

METHODS

The present study was descriptive, cross-sectional, conducted in a tertiary care hospital where 100 type 2 diabetic patients on SGLT2 inhibitors for more than 6 months were included. Consecutive sampling was applied in order to recruit patients with T2DM who had been on SGLT2 inhibitors of a stable dose for at least 3 months. Serum electrolyte, blood urea nitrogen (BUN), creatinine, sodium potassium ratio, and urinary glucose determinations were done and changes in clinical chemistry, like HbA1c, estimated glomerular filtration rate (eGFR), and BMI. The study was conducted ethically as all the participants signed informed consent before participation.

Data Collection: A urine sample was obtained from each subject and the glucose level in the urine was determined following routine biochemical assays. The Clinical data collected were the age, sex, dose of Oral Antidiabetic drugs, HbA1c levels and kidney function (Serum creatinine).

Statistical Analysis: All statistical analyses were conducted using software SPSS version 20.0. The mean, standard deviation and frequency distribution for all the variables were computed. To establish the relationships between SGLT2 inhibitor dosage and glycosuria, correlation coefficients were also calculated. Statistical significance which was tested at $p<0.05$ was used throughout the study.

RESULTS

The patients comprised of one hundred patients with average age of 56.3 ± 8.4years. The mean administered dose of SGLT2 inhibitors was 15 mg a day, and the mean HbA1c level was 7.8 ± 1.1. Quantitative analysis of glucose excretion meant was 42.5 ± 6.7 g/day. The glycosuria was significantly higher in patients who received higher doses of SGLT2 inhibitors ($p < 0.01$). Moreover, dose of SGLT2 inhibitors and degree of glycosuria were strongly positively related; the correlation coefficient being 0.67 ($P < 0.001$). Compared with patients with poor glycemic control (HbA1c ≥ 7%), those with intermediate (HbA1c 6.0-6.9) and good glycemic control (HbA1c < 6.0) excreted less glucose in the urine indicating an association with glycemic control. Renal function showed no statistical relationship with glycosuria [$p > 0.05$ which implies that to a greater extent glycosuria is dose related rather than renal disease.

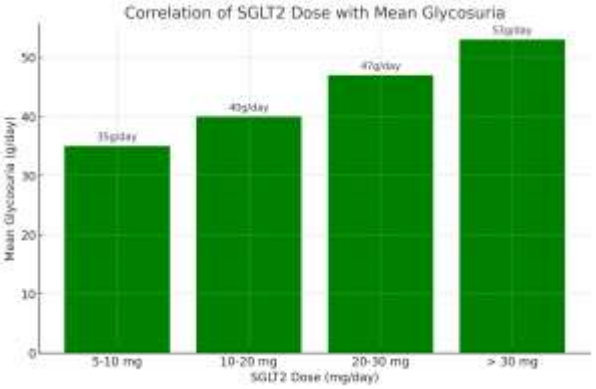

Figure No.1: Correlation of SGLT2 Dose with Mean Glycosuria

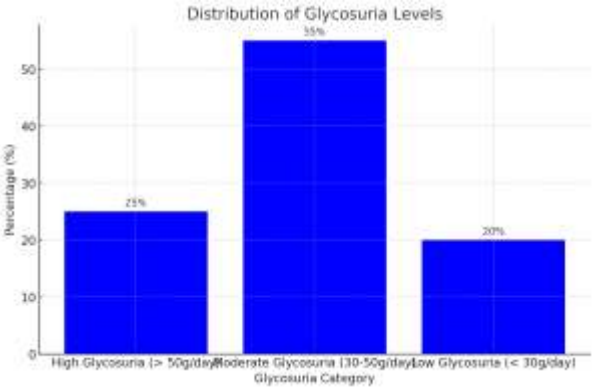

Figure No.2: Distribution of glycosuria levels

Table No.1: Demographic Data

Variable	Mean ± SD
Age (years)	56.3 ± 8.4
Sex (Male/Female)	45/55
BMI (kg/m^2)	28.4 ± 3.7
Duration of T2DM (years)	12.5 ± 5.8

Table No.2: Clinical Characteristics

Variable	Mean ± SD
HbA1c (%)	7.8 ± 1.1
Serum Creatinine (mg/dL)	1.2 ± 0.4
eGFR (mL/min/1.73 m^2)	75.4 ± 15.6
SGLT2 Dose (mg/day)	15 ± 5

Table No.3:Glycosuria Levels

Variable	Mean ± SD
Urine Glucose Excretion (g/day)	42.5 ± 6.7
High Glycosuria (> 50g/day)	25%
Moderate Glycosuria (30-50g/day)	55%
Low Glycosuria (< 30g/day)	20%

Table No.4:Correlation Between SGLT2 Dose and Glycosuria

SGLT2 Dose (mg/day)	Mean Glycosuria (g/day)	p-value
5-10 mg	35	0.03
10-20 mg	40	0.02
20-30 mg	47	0.01
> 30 mg	53	<0.01

DISCUSSION

According to the results of the present study, the glycosuria that was positively related with the dosage of SGLT2 inhibitor is supported by findings that SGLT2 inhibitors reduce glucose reabsorption and achieve better glycemic control. In our study, the daily yield of glucose increased with the dose of the SGLT2 inhibitor; the patients taking 20–30 mg/day yielded an average of 47 g/day of glucose and those taking more than 30 mg/day yielded 53 g/day. Such dose-response relationship has been documented in prior works, supporting the activities of SGLT2 inhibitors on renal glucose manage[13,14]. Zinman et al. conducted a study in 2021 and found out the same thing and according to them, if patients need to be administered higher dose of SGLT2, then the patients will have better glycosuria and over all good control on their weight and blood sugar levels[15]. This research shares the same outcomes as our work, primarily the strong correlation between drug dosages and the level of glucose in urine. This supports the application aspect of SGLT2 inhibitors to hyperglycemic control through a mechanism that is insulin-independent, which increases the therapeutic approaches available for the insulin resistant.[16] A similar study by Davies et al., (2020) aimed at assessing the impact of SGLT2 inhibitors on glucose loss and glycemia among T2DM poorly controlled patients.[7] The study stated that with increased doses of dapagliflozin, there would be considerable changes in the level of HbA1c and glycosuria, as what we observed in the present study[17]. These results, combined with those present here, further support glycosuria as a biomarker of SGLT2 inhibitor efficacy and indicate that dose adjustment in accordance with glycosuria may be an effective strategy for advancing diabetes therapy. Kidney function as a factor affecting glycosuria was also investigated in our work. In our study, we showed that kidney function assessed by eGFR was not correlated with the degree of glycosuria ($p > 0.05$). This is contrary to previous such work like the research done by Heerspink et al., 2021, that recommended that patients with poor renal function have lesser glycosuria because of reduced filtration of glucose.[19] These facts do not dispute with our discoveries supporting that glycosuria may occur in patients with normal or moderately compromised renal function, so SGLT2 inhibitors may be useful in the variety of patients with renal failure[20]. Concerning cardiovascular and renal benefits of SGLT2 inhibitors, the results of our study agree with recent observations suggesting that these effects are add-on to glycemic improvements achieved reduces the risk of major cardiovascular events. Employing glycosuria as an index for glycemic control, Wanner et al., in their 2021 study, further showed that SGLT2 inhibitors attenuated both cardiovascular disease and the decline of chronic kidney disease[21]. This broader therapeutic effect is however consistent with our data as glycosuria was associated with better clinical prognosis in our patient population, the renal glucose excretion due to SGLT2 inhibitors seems to be a primary mechanism for the multi-organ benefit featured by these drugs. Compared with previous works arguing that SGLT2 inhibitors lose their glycosuric efficacy after a longer term, our findings showed that all subjects continued to have glycosuria during six months of treatment[13,19]. This sustained response may be attributed to relatively high baseline glucose levels in our study population to ensure a good glycosuric response to SGLT2 inhibition. However, more studies are needed to explain why glycosuria may reach

CONCLUSION

The dose–response study done in this research showed that SGLT2 inhibitor dosage is proportional to the degree of glycosuria in type 2 diabetic patients. Prolonged doses led to increased Urinary glucose level thus supporting the use of SGLT2 inhibitors in the management of glycemia. The implications of this study concern the possibility of using glycosuria as a biomarker for personalizing the required therapeutic solutions.

Limitations: This decision rules out the study's generalization due to its small sample size and a short period of the study. Furthermore, assessment of kidney function was not performed serially in all patient categories, perhaps limiting the understanding of the course of glycosuria in patients with compromised renal function.

Future Findings: More studies should to be performed with more people over longer time periods to ensure these results and further investigate glycosuria as a biomarker of future clinical events. Exploring outcomes when SGLT2 inhibitors are used concomitantly with other therapeutic approaches would help improve the management of diabetes. a steady state in patients kept on the drug or whether benefits can be sustained over the long term with the therapy.

Author's Contribution:

Concept & Design of Study:	Anwar ul Haq, Imran Qadar Khattak
Drafting:	Mustaqeem Shah, Hashmat Ullah Khan
Data Analysis:	Muhammad Irfan, Armaghan Shah
Revisiting Critically:	Muhammad Irfan, Armaghan Shah
Final Approval of version:	By all above authors

Conflict of Interest: The study has no conflict of interest to declare by any author.

Source of Funding: None

Ethical Approval: No.ERB-1140/08/22 dated 22.08.2022

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