RESEARCH ARTICLE

Dysregulated renal tubular handling of filtered glucose in patients with type 2 diabetes mellitus: A descriptive study

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Abstract

Objective: To determine the frequency of suspected dysregulated renal tubular handling of filtered glucose, and its association with blood glucose levels in type 2 diabetes mellitus.

Method: The analytical, cross-sectional study was conducted from November 2022 to June 2023 at the Department of Medicine along with the Department of Pathology and Biochemistry, Pakistan Railway Hospital, Islamic International Medical College, Rawalpindi, Pakistan, and comprised diabetics aged 19-80 years. Blood and urinary glucose were assessed at the point of contact. Blood glucose 80-180mg/dl was considered glucose in range and >180mg/dl glucose above range. Hyper-function of sodium glucose transport receptors was suspected if urinary glucose was <++ and the function of these receptors was considered normal if urinary sugar was ++ or more. Association of suspected receptors functioning and their association with blood glucose levels was determined. Data was analysed using SPSS 26.

Results: Of the 159 diabetics, 91(57%) were females and 68(43%) were males. The overall mean age was 57±11 years (range: 46-68 years). Of the total, 43(27%) patients had glucose in range and 116(73%) had glucose above range. Of the diabetics with glucose above range, 54(47%) patients had hyper-functioning sodium glucose transport receptors, and 62(53%) had normal functioning sodium glucose transport receptors. Of the patients with glucose in range, 11(26%) had hyper-functioning sodium glucose transport receptors, and 32(74%) had normal functioning sodium glucose transport receptors. There was a significant association between sodium glucose transport receptors' function and blood glucose levels ($p<0.001$).

Conclusion: Dysfunction of sodium glucose transport receptors affected the secretion of glucose in the urine, resulting in impaired glucose regulation in type 2 diabetes mellitus cases.

Keywords: Blood glucose, Diabetes, Glycosuria, Sodium-glucose transporter 2. (JPMA 74: 1986; 2024)

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, multifactorial and heterogeneous metabolic disorder involving dynamic interactions between environmental factors and gene susceptibility.[1] In the next 20 years, the prevalence of T2DM may increase due to population growth, increasing obesity, sedentary lifestyle and other as-yet-unidentified causes. According to the International Diabetes Federation (IDF), Pakistan ranks third in the world for diabetes prevalence, following China and India. Approximately 33 million individuals in Pakistan are living with diabetes.[2] Through the mechanisms of glucose filtration, glucose reabsorption and gluconeogenesis, the kidneys assist in the maintenance of glucose homeostasis. Changes in any of these systems can occur in T2DM patients, making them potential candidates for novel treatments, like inhibition of renal reabsorption of glucose by sodium-glucose co-transporter inhibitors (SGLT2i).[3] The primary pathway for renal glucose reabsorption is the sodium glucose co-transporter SGLT2 in the early proximal tubule, and SGLT2 inhibition lowers plasma glucose levels, improves glycaemic control in all stages of DM and can be taken with other anti-diabetic medications.[4]

If SGLT2 receptors are hyperactive, all the filtered glucose gets reabsorbed. In patients with T2DM, the renal threshold for blood glucose is raised from 180 to 250, thus contributing to hyperglycaemia, and in oder to normalise the renal threshold back to 180, SGLT2 receptor inhibitors are used. SGLT2 inhibitors can exert their anti-hyperglycaemic effects in conjunction with any other oral anti-diabetic medication in addition to insulin.[5]

Renal tubular handling of the filtered glucose is through SGLT2 receptor functioning. To some extent, SGLT2 receptor functioning can be assessed by monitoring glycosuria in urine routine examination, and co relating it with adequacy of glycaemic control in a simultaneous point of contact blood sample. If in T2DM, urinary sugar is

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high (arbitrarily defined as urinary sugar >++), it means SGLT2 receptors are not hyper-functioning, and, as such, the role of SGLT2 inhibitors is less for glycaemic control in this subset of patients, but can be used for its benefits beyond glycaemic control, like cardio-renal protection.[6,7] If in T2DM, urinary sugar is low (arbitrarily defined as urinary sugar ++ or less), it means SGLT2 receptors are hyper-functioning, and, as such, in this subset of patients, the role of SGLT2 receptor inhibition will be most beneficial for glycaemic control.

Among the diabetics, glycosuria has been considered a significant biomarker for poor glycaemic control.[8] However, diabetologists are now reassessing glycosuria as an alternative biomarker to improve glycaemic control, and avert renal and cardiovascular consequences by administering SGLT2 inhibitors. The adequacy of urinary glucose excretion in relation to glycaemic levels need to be studied in the Pakistani population to predict the subset of T2DM patients who will be benefitted most with the addition of SGLT2 receptor inhibitors in their pharmacotherapy. Person-to-person variations are frequently seen in the amount of urinary glucose excretion and the effectiveness of SGLT2 inhibitors.[9,10] Although SGLT2 receptor function is significantly associated with blood glucose levels in patients with T2DM, there is a research gap on using baseline assessments of SGLT2 receptor functionality to guide treatment choices. The current study was planned to determine the frequency of suspected dysregulated renal tubular handling of filtered glucose, and its association with blood glucose levels in T2DM patients.

Patients and Methods

The analytical, cross-sectional study was conducted from November 2022 to June 2023 at the Department of Medicine along with the Department of Pathology and Biochemistry, Pakistan Railway Hospital, Islamic International Medical College, Rawalpindi, Pakistan. After approval from the Riphah International University's ethics review committee, the sample size was calculated using the University of California, San Francisco, (UCSF) calculator[11] with α=0.05, β=0.20 and r=0.22.[12] The sample was raised using non-probability convenience sampling technique. Those included were diabetics of either gender aged 19-80 years. Those excluded were type 1 diabetes patients, those with chronic kidney disease (CKD) having estimated glomerular filtration rate (eGFR) <45, and significant proteinuria with greater >+ on urine dipstick, or any other significant comorbidity, like advanced malignancy, decompensated cirrhosis, and advanced respiratory diseases. T2DM patients on SGLT2 inhibitors were also excluded.

After taking informed consent, Demographic and clinical data, including age and body mass index (BMI), was recorded.

Blood and urinary glucose were assessed at the point of contact for which 5ml venous blood was drawn by aseptic measures in sodium fluoride (NaF) tubes. The blood samples were centrifuged for 5 minutes at 3,000 revolutions per minute (rpm). Plasma glucose was estimated by the glucose oxidase method on an automated analyzer (Selectra Pro M, ELITechGroup, Puteaux, France) using the relevant reagent (Merck, Darmstadt, Germany). Semi-quantitative urine glucose estimation of the patients was done with urine dipsticks (Combi 10, Rosche Diagnostics, Pakistan). Blood glucose 80-180mg/dl was considered glucose in range (GIR) and >180mg/dl glucose above range (GAR). Hyper-function of SGLT2 receptors (HSLGT2) was suspected if urinary glucose was ++ or less, and the function of these receptors was considered normal (NSLGT2) if urinary sugar was ++ or more. The association of HSGLT2 resulting in GAR and NSGLT2 leading to GIR was determined.

Data was analysed using SPSS 26. Data normality was assessed using Shapiro-wilk test. Demographic variables were expressed as frequencies and percentages, while continuous variables were expressed as mean ± standard deviation. Chi square test was used to ascertain various associations. P< 0.05 was considered significant.

Results

Of the 159 diabetics, 91(57%) were females and 68(43%) were males. The overall mean age was 57±11 years (range: 46-68 years). Mean BMI was 25.98±4.98kg/m^2 (range: 21-30.96kg/m^2). There were 49(31%) patients who had onset of T2DM <5 years ago, while 110(69%) patients were diagnosed with T2DM >5 years ago. Mean eGFR was 60.53±11.9ml/min/1.73m^2 (range: 49-72ml/min/1.73m^2). Mean blood pressure (BP) was 117/67±14.7/9.9mmHg (range: 100/70-190/110mmHg) (Table 1).

Of the total, 43(27%) patients had GAR and 116(73%) had GIR. Of the diabetics with GAR, 54(47%) had HSLGT2, and 62(53%) had NSLGT2. Of the patients with GIR, 11(26%) had

Table-1: Demographic and biochemical parameters of the participants (n= 159).

Variables	Mean±SD
Age (years)	57.97±11.59
BMI: (kg/m^2)	25.98±4.98
BP (mmHg)	140/90±15/10
eGFR: (ml/min/1.73m^2)	60.53±11.9
Gender	n (%)
Male	68 (43)
Female	91 (57)
Onset of diabetes	
< 05 years	49 (31)
> 05 years	110 (69)

eGFR: Estimated glomerular filtration rate, BMI: Body mass index, BP: Blood pressure, SD: Standard deviation.

Table-2: GIR, GAR, HSGLT2and NSGLT2 values among T2DM patients.

Blood Glucose Levels	n (%)	Urinary Glucose	n (%)	Urinary Glucose (≤ ++) (HSGLT2 receptors) n (%)	Urinary Glucose (> ++) (NSGLT2 receptor) n (%)
GIR: <180mg/dl	43 (27)	-	-	11 (26)	32 (74)
		Trace	2 (1.25)		
		+	5 (3.14)		
		++	4 (2.51)		
		+++	27 (17)		
		++++	5 (3.1)		
GAR: >180mg/dl	116 (73)	Nil	17 (11)	54 (47)	62 (53)
		Trace	5 (3)		
		+	16 (10)		
		++	16 (10)		
		+++	35 (22)		
		++++	27 (17)		

GIR: Glucose in range, GAR: Glucose above range, HSGLT2: Hyper-functioning of sodium glucose transport receptors, NSGLT2: Normal functioning of sodium glucose transport receptors, T2DM: Type 2 diabetes mellitus.

Table-3: Association of blood glucose with urinary glucose in T2DM patients.

Blood Glucose Level	Urinary Glucose (≤++) (HSGLT2 receptors) n (%)	Urinary Glucose (>++) (NSGLT2 receptors) n (%)	Total n (%)	X^2	df	*p*-value
GIR: <180mg/dl	11 (26)	32 (74)	43 (27)	13.3	1	<0.001
GAR: >180mg/dl	54 (47)	62 (53)	116 (73)			

GIR: Glucose in range, GAR: Glucose above range, HSGLT2: Hyper-functioning of sodium glucose transport receptors, NSGLT2: Normal functioning of sodium glucose transport receptors, T2DM: Type 2 diabetes mellitus.

HSLGT2, and 32(74%) had NSLGT2 (Table 2).

There was a significant association between SGLT2 receptors' function and blood glucose levels ($p<0.001$) (Table 3).

Discussion

SGLT2 inhibitors (SGLT2Ri) are an important addition in the pharmacotherapy of T2DM. These drugs not only have a role in controlling hyperglycaemia, but also help achieve BP control, and have been identified to have a very important role in cardio-renal protection.[13] Their beneficial role in cardiac failure and diabetic nephropathy is also well established. Use of SGLT2Ri in diabetic patients has increased a lot, but the drug also has important side effects, like pelvic or urinary tract infections (UTIs), urosepsis, hyponatraemia, euglycemic ketoacidosis etc.[14] These drugs should be prescribed cautiously and to the subset of patients in whom these can be most effective in achieving glycaemic targets. The present study identified the subset of patients having dysregulated renal tubular handling of filtered glucose as these patients stand to benefit the most with SGLT2Ris. In the present study, 47% of patients having GAR presented with HSGLT2 receptors. These are the patients who are most likely to be benefited by SGLT2Ri, while 53% of the patients had NSGLT2 receptor functioning in whom SGLT2Ris are not indicated as first-line glycaemic control, but they can be used for benefits beyond glycaemic control. In the present study, patients with GIR had better glucose control. Conversely, patients with GAR poor glucose control. The findings of showed that the frequency of SGLT2 receptor functions had an association with glycaemic control. One-third of the current patients stood to benefit from SGLT2Ris. It is well established that diabetic patients do not typically have glycosuria at plasma glucose levels that non-diabetics would due to an increase in the reabsorption of glucose from glomerular filtrate in T2DM patients.[15,16] A study indicated that mean plasma glucose level strongly influenced urine glucose excretion, which was consistent with the current findings.[17] Urinary glucose correlated positively with fasting and random blood glucose, and the finding was consistent with several studies.[18] According to Bonner et al., T2DM patients have lower blood glucose after administering SGLT2Ri because their glycosuria increased compared to placebo recipients, creating a more favourable homeostatic window for serum glucose levels.[19] As the urinary glucose excretion increases, the plasma glucose levels fall, leading to improvement in all glycaemic parameters.[20] This finding supported the current study, suggesting that HSGLT2 may contribute to poor glycaemic control. Another study documented that urinary glucose correlated significantly with glycaemic control ($p<0.001$) in diabetic population,[18] which was also shown by the current study. Previous studies indicated that as the urinary glucose excretion increased, the plasma glucose levels fell, leading to improvement in all glycaemic parameters.[21] This finding aligned with the current results.

Patients with diabetes who were given an SGLT2 inhibitor in a randomised controlled trial (RCT) demonstrated improved glycaemic control and a decrease in glycated haemoglobin (HbA1c) levels.[22] This strengthens the current results that targeting the SGLT2 receptor may have therapeutic benefits for improving glucose management in T2DM.

Steven S. et al. stated that activating the SGLT2 receptor enhanced glucose uptake and increased hyperglycaemia, which is in line with the current findings.[23]

The current study also suggested that not all the patients having GAR had HSGLT2. As such, only those patients who have HSGLT2 status on baseline lab assessment should be prescribed SGLT2Ri as first-line treatment. In other patients, SGLT2Ri should be used cautiously for benefits beyond glycaemic control.

The current study has limitations as it estimated semi-quantitative urine glucose using urine dipsticks. Preferably, urinary glucose levels should have been measured quantitatively to produce more precise and accurate results. Additionally, HSGLT2 was inferred based on semi-quantitative urine dipstick results, which decreases the scientific integrity of the findings. The analysis should have involved quantitative real-time polymerase chain reaction (RT-PCR) to determine messenger ribonucleic acid (mRNA) of the SGLT2 receptor transport protein. Besides, the study has a small sample size and the data relates to a single centre. Further research across diverse demographics under varied conditions and diverse clinical settings is essential to validate the current findings.

Conclusion

There was a significant association of SGLT2 receptors' function and blood glucose levels in T2DM patients, indicating that the dysfunction of SGLT2 receptors affected the secretion of glucose in the urine, resulting in impaired glucose regulation in T2DM patients.

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Author Contribution:

AZ: Concept, data collection, and revision.
SJ: Acquisition, analysis, interpretation and drafting.
MNAK: Design, analysis and revision.
SB: Data collection, interpretation and revision.
MF, KF: Design, data collection and revision.
All the author involved in final approval and agreement to be accountable for all the aspects of the work.