

A Case of Isolated Glycosuria Mediated by an *SLC5A2* Gene Mutation and Characterized by Postprandial Heavy Glycosuria Without Salt Wasting

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Familial renal glycosuria (FRG) is an inherited disorder characterized by persistent glycosuria in the absence of hyperglycemia. It is caused by mutations in the sodium-glucose co-transporter, leading to increase in the renal excretion of glucose and sodium. However, there have been no studies on the role of fasting and postprandial changes in the urinary sodium excretion in patients with FRG. We report a case of renal glycosuria, which was confirmed by a *SLC5A2* mutation via gene sequencing, and compared the postprandial urinary glucose and sodium excretion. A 26-year-old man sometimes experienced glycosuria on routine screening; however, other laboratory findings were normal. His fasting and postprandial urinary glucose excretion levels were 295 mg/dL and 2,170 mg/dL, respectively. The fasting and postprandial urinary sodium excretion levels were 200 mEq/L and 89 mEq/L, respectively. In patients with FRG, excessive diuresis might be prevented by a compensatory mechanism that reduces postprandial sodium excretion.

Key Words: Renal glycosuria, Sodium glucose cotransporters, Renal excretion

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Introduction

Isolated glycosuria is a non-disease condition characterized by increased urinary glucose excretion but a normal serum glucose level. Familial renal glycosuria (FRG) is an inherited renal tubular disorder in which there is persistent isolated glycosuria in the absence of hyperglycemia. It is caused by mutations in *SLC5A2*, the gene encoding the sodium glucose co-transporter (SGLT2). SGLT2 inhibition increases the renal excretion of glucose and sodium, thereby lowering the serum glucose level and reducing the plasma volume¹⁾. Although enhanced sodium excretion is thought to contribute to the reduction in plasma volume and lowering of the blood pressure (BP), clinical data on urinary sodium excretion in FRG are limited²⁾. There have

also been no studies on the role of fasting and postprandial changes in urinary sodium excretion in patients with FRG. Here, we report a case of isolated renal glycosuria in a healthy young man with an *SLC5A2* gene mutation. In this patient, we investigated the change in the urinary Na⁺/glucose concentration after glucose loading to evaluate the tubular glucose and sodium reabsorption capacity in FRG.

Case Report

A 26-year-old man visited our outpatient clinic for the evaluation of incidentally found glycosuria. The patient was a healthy military officer in whom glycosuria, but no other abnormal lab findings, was detected on repeated routine screening. He had no manifestation of renal disease and was not taking any medication. His mother had

the same history of incidental glycosuria on routine screening. Neither an examination of his physiological systems nor physical examination revealed any abnormal finding. His laboratory results did not indicate tubular dysfunction, except renal glycosuria, or any other condition that could contribute to his hyperglycemia. His fasting blood glucose level was 84 mg/dL, PP2 glucose level was 126 mg/dL, and HbA1C level was 5.4%. His blood urea nitrogen and creatinine levels were 13.3 and 1.21 mg/dL, respectively. Dipstick urinalysis showed 4+ glucose, pH 5.0; however, blood and protein were absent. His 24-h urinary glucose level was 3,700 mg, and creatinine excretion level was 1.71

g/day. An examination of the patient for fasting and postprandial changes in urinary glucose and electrolytes showed fasting spot urinary glucose level of 295 mg/dL and PP2 urinary glucose level of 2,170 mg/dL. Fasting and postprandial urinary sodium excretion levels were 200 mEq/L and 89 mEq/L, respectively (Fig. 1). Fasting and postprandial urinary osmolarities were 902 mOsm/kg and 834 mOsm/kg, respectively. Sequencing of the patient's *SLC5A2* gene showed a heterozygous missense mutation of c.395 G>A in exon 4 that resulted in the replacement of an arginine with a histidine at position 132 (p.R132H) of the protein (Fig. 2).

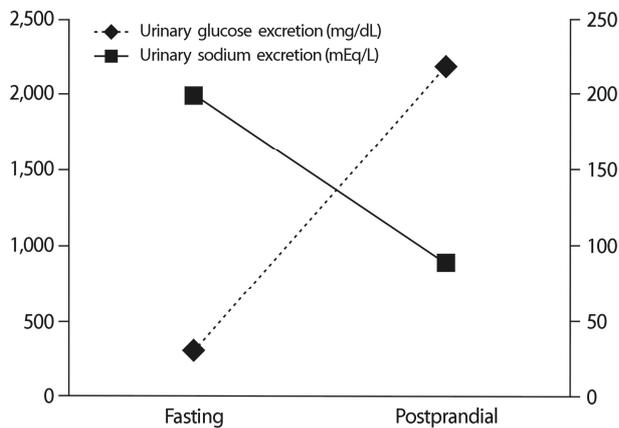


Fig. 1. Changes in the fasting and postprandial urinary sodium and glucose excretion in a patient with familial renal glycosuria.

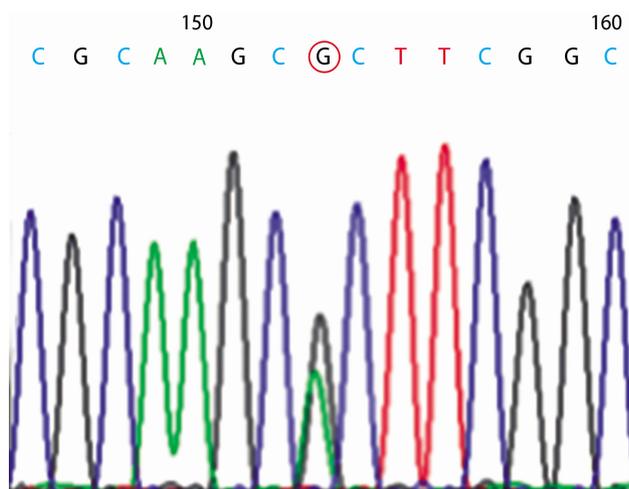


Fig. 2. Sequence analysis of exon 4 of the SGLT2 gene from the study patient. Circles indicate the c.395 position, showing a heterozygous alteration of G>A.

Discussion

Under normal physiological conditions, the kidney reabsorbs all of the filtered glucose via the proximal tubule, in a process mediated by *SGLT2*, a kidney-specific, low-affinity/high-capacity Na⁺/glucose co-transporter. A defect in this transporter causes glycosuria³. The *SLC5A2* gene encodes SGLT2, and mutations in *SLC5A2* are responsible for renal glycosuria, and it is commonly associated with FRG⁴. The first report of an *SLC5A2* mutation in FRG was published in 2000⁴. Subsequently, another study with a larger number of patients confirmed that *SLC5A2* mutations are responsible for the vast majority of FRG cases⁵. Our patient was heterozygous for the missense mutation c.395 G>A in exon 4, causing the substitution of histidine for arginine at position 132 (p.R132H) in the protein. This allele has been previously reported⁶.

FRG is an inherited renal tubular disorder characterized by persistent isolated glycosuria in the absence of hyperglycemia. The safe and normal lives of patients with FRG accelerated the development of SGLT2 inhibitors. An emerging new class of oral antidiabetic drugs, SGLT2 inhibitors, significantly reduced not only HbA1C level but also systolic BP in obese patients with type 2 diabetes mellitus. One suggested mechanism is that SGLT2 inhibitors decrease BP via osmotic diuresis induced by urinary glucose and sodium excretion and loss of body weight¹. Our patient had a fasting urinary sodium excretion level of 200 mEq/L; however, his postprandial urinary sodium excretion level

was 89 mEq/L. There is no previous report of fasting and postprandial differences in the urinary sodium concentration of patients with FRG. We think that the mechanism underlying this difference may be a compensatory one, protecting against osmotic diuresis induced by the increased excretion of glucose in the urine. It likely involves an increase in the sodium reuptake at the loop of Henle and at more distal tubules. However, further studies on both urinary sodium and glucose excretion in patients with FRG are required.

Conclusions

Patients with FRG have a good renal prognosis despite constant renal glucose and sodium loss. Excessive diuresis might be prevented by a compensatory mechanism that reduces postprandial sodium excretion.

Conflict of Interest: The authors declare no relevant financial interests.

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