CLINICAL VIGNETTE

A Case of Congenital Benign Renal Glycosuria Likely Caused by Genetic SGLT2 Mutation

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A 51-year-old female with chronic yeast infections and multiple urinary tract infections was referred to nephrology for glycosuria. Her fasting blood sugars have been slowly increasing towards 100mg/dL. She has prehypertension and history of paroxysmal supraventricular tachycardia, well controlled on beta-blockers. She had been evaluated in the past because both her mother and sister had renal glycosuria, and was advised it was benign without need for further follow up. Serum BMP, phosphorus, and urinary pH were all within normal limits. Her fasting and non-fasting blood sugars were between 90 and 120 mg/dL and never exceeded the tubular maximum of 180 mg/dL expected before glycosuria manifests. A random urine glucose level was 160 mg/dL, which was greater than the serum glucose level.

She had multiple urinary tract infections consistent with the presentation usually seen with patients on gliflozins, but without acute kidney injury or chronic kidney disease, as is sometimes a risk in patients on SGLT-2 antagonists. Despite the glycosuria, the patient's prediabetes has worsened. Figure 1 presents a graphical trend of glycosuria and electrolytes. Figure 2 depicts the mechanism of SGLT 2 function in the renal proximal convoluted tubule.

Diabetes management is experiencing a wave of innovation with the addition of the gliflozin class of anti-hyperglycemic agents. These drugs are currently used in conjunction with metformin, thiazolidinediones, gliptins, and sulfonylureas to help control blood sugar without the need for injectable agents (like insulin and incretin mimetics).[1,2] Given the increased microvascular[3] and cardiovascular risks with diabetes,[4] the decrease in cardiovascular events among patients treated with gliflozins is encouraging.[5-8] The new agents seen are not without risks. These include lactic acidosis, urinary tract infections, and acute kidney and chronic kidney disease. These risks were recently reiterated by the Food and Drug administration (FDA).[9]

The gliflozins are antagonists of SGLT2 (sodium glucose linked transporter). These transporters are a family of channels that couple sodium movement across its chemical gradient to power glucose symport into cellular cytoplasm against its concentration gradient. They are expressed in the latter part of the proximal convoluted tubules (PCT) where they are involved in glucose reabsorption from filtered plasma. Gliflozins inhibit this target to increase glucose excretion and help lower serum glucose levels in diabetics. The gliflozins produce isolated glycosuria, whereas other proximal tubular dysfunction syndromes cause aminoaciduria, bicarbonaturia, and phosphaturia. The bicarbonaturia noted with PCT dysfunction is due to proximal renal tubular acidosis (type II). Fanconi's syndrome usually results in the former acidosis as well as aminoaciduria and concomitant phosphaturia with hypophosphatemia due to global PCT dysfunction. Conditions like multiple myeloma and medications such as topiramate, acetazolamide, and tenofivir can also cause proximal convoluted tubular dysfunction.[10] This is in opposition to the urinary profile of glifzolins, which cause glycosuria alone.

Table 1 lists medication induced, genetic, and acquired causes of proximal convoluted tubular dysfunction.

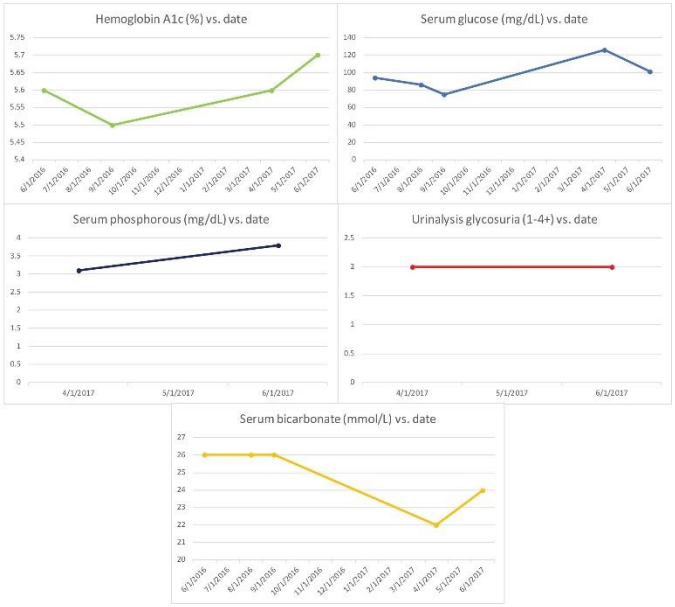

Figure 1 - Graph of RUA measurement of glycosuria as measured on routine urinalysis vs. date, serum glucose levels in mg/dL vs. date, serum Hco3 mmol/L vs. date, serum phosphorous mg/dL vs. date, and hemoglobin a1c (%) vs. date.

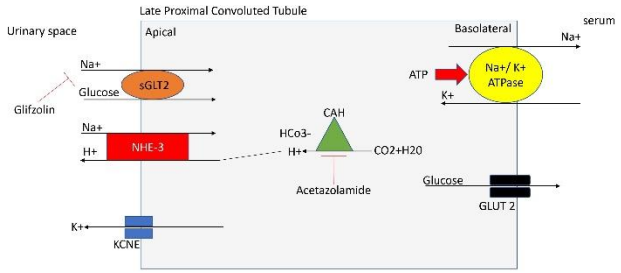

Figure 2 - Schematic of proximal convoluted tubule function in its three segments ATP=adenosine triphosphate, CAH=Carbonic anhydrase inhibitor, CO2=carbon dioxide, GLUT2= glucose channel basolateral membrane, H20=water, H+=proton, Hco3=bicarbonate, K+=potassium, KCNE=voltage gated potassium channel, Na+=sodium, NHE-3= sodium proton antiporter , SGLT2= sodium glucose linked transporter 2.

Table1: Causes of Proximal convoluted tubule dysfunction	
Genetic	**pattern**
heridtary cystinosis	Fanconi's
tyrosinemia	Fanconi's
galactosemia	Fanconi's
glycogen storage diseases	Fanconi's
heridtary fructose intolerance	Fanconi's
Dent's disease	Fanconi's
Medications	**pattern**
acetazolamide	isolated type II RTA
topiramate	isolated type II RTA
tenofivir	varies, isolated glycosuria up to full fanconi's syndrome
Glifzolin class	isolated glycosuria
Expired tetracyclines	Fanconi's
Acquired disease	**pattern**
Multiple myeloma/Monoclonal gammopathy	RTA, proteinuria
Lead poisoning	Fanconi's
Sjogren's syndrome	Fanconi's
Pleuritis and other auto immune disease	Fanconi's

Table 1 - Causes of genetic, acquired, and medication induced proximal convoluted tubular dysfunction.

Conclusions

This patient has isolated glycosuria without hypophosphatemia, acidosis (especially a renal tubular acidosis of proximal type), or Fanconi's syndrome that is generally seen in global proximal convoluted tubular dysfunction. Glycosuria may be protective given her comorbid pre-hypertension and prediabetes. It is important to distinguish benign renal glycosuria from a medication effect, Fanconi's syndrome, and proximal renal tubular acidosis due to myeloma. The patient is considering genetic testing to define if SGLT2 or another closely related protein is the causative agent of her glycosuria, though her clinical course will be quite benign with a favorable long term renal prognosis.

REFRENCES

1. **Stein SA, Lamos EM, Davis SN**. A review of the efficacy and safety of oral antidiabetic drugs. *Expert Opin Drug Saf*. 2013 Mar;12(2):153-75. doi: 10.1517/14740338.2013.752813. Epub 2012 Dec 14. Review. PubMed PMID: 23241069; PubMed Central PMCID: PMC3977601.
2. **Lamos EL, Stein SA, Davis SN**. Sulfonylureas and meglitinides: historical and contemporary issues. *Panminerva Med*. 2013 Sep;55(3):239-51. Review. PubMed PMID: 24088798.
3. **Konig M, Lamos EM, Stein SA, Davis SN**. An insight into the recent diabetes trials: what is the best approach to prevent macrovascular and microvascular complications? *Curr Diabetes Rev*. 2013 Sep;9(5):371-81. Review. PubMed PMID:23865412.
4. **Bertoluci MC, Rocha VZ**. Cardiovascular risk assessment in patients with diabetes. *Diabetol Metab Syndr*. 2017 Apr 20;9:25. doi: 10.1186/s13098-017-0225-1. eCollection 2017. Review. PubMed PMID: 28435446; PubMed Central PMCID:PMC5397821.
5. **Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators**. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015 Nov 26;373(22):2117-28. doi: 10.1056/NEJMoa1504720. Epub 2015 Sep 17. PubMed PMID: 26378978.
6. **Zinman B, Lachin JM, Inzucchi SE**. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2016 Mar 17;374(11):1094. doi: 10.1056/NEJMc1600827. PubMed PMID: 26981940.
7. **Inzucchi SE, Zinman B, Wanner C, Ferrari R, Fitchett D, Hantel S, Espadero RM, Woerle HJ, Broedl UC, Johansen OE**. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. *Diab Vasc Dis Res*. 2015 Mar;12(2):90-100. doi: 10.1177/1479164114559852. Epub 2015 Jan 14. Review. PubMed PMID: 25589482; PubMed Central PMCID: PMC4361459.
8. **Abdul-Ghani M, Del Prato S, Chilton R, DeFronzo RA**. SGLT2 Inhibitors and Cardiovascular Risk: Lessons Learned From the EMPA-REG OUTCOME Study. *Diabetes Care*. 2016 May;39(5):717-25. doi: 10.2337/dc16-0041. PubMed PMID: 27208375; PubMed Central PMCID: PMC4839176.
9. **Desai M, Yavin Y, Balis D, Sun D, Xie J, Canovatchel W, Rosenthal N**. Renal safety of canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2017 Jun;19(6):897-900. doi: 10.1111/dom.12876. Epub 2017 Mar 16. PubMed PMID: 28083972; PubMed Central PMCID:PMC5485046.
10. **Haque SK, Ariceta G, Batlle D**. Proximal renal tubular acidosis: a not so rare disorder of multiple etiologies. *Nephrol Dial Transplant*. 2012 Dec;27(12):4273-87. doi: 10.1093/ndt/gfs493. Review. PubMed PMID: 23235953; PubMed Central PMCID: PMC3616759.

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