Kidney Medicine

SGLT2 Inhibitor Use for Treatment of Hypocitraturia in a Distal Renal Tubular Acidosis

Stefan Scherr, Sara H. Ksiazek, Christoph Schwarz, and Marcus D. Säemann

5-Amino salicylic acid (5-ASA) is a known culprit for the development of tubulointerstitial nephritis. Together with impaired kidney function, tubulointerstitial nephritis can lead to specific tubular malfunctions including distal renal tubular acidosis. Distal renal tubular acidosis is an acid-base disorder in which acid secretion in the distal part of the renal tubular system is decreased. Patients with distal renal tubular acidosis are predisposed to recurrently form calcium phosphate kidney stones. This results from the inability to acidify the urine properly as well as from a decreased citrate concentration in the urine, which is another pathognomonic feature of distal renal tubular acidosis. We present the case of a man in his late 40s with Crohn's disease who developed tubulointerstitial nephritis associated with 5-ASA leading to the development of distal renal tubular acidosis and recurrent calcium phosphate nephrolithiasis. After steroid therapy and partial recovery of kidney function, we observed an increase of citraturia in response to treatment with dapagliflozin, potentially indicating beneficial effects of sodium/glucose cotransporter 2 inhibition on the recurrence of calcium phosphate stone disease in interstitial nephritis-induced distal tubular acidosis.

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INTRODUCTION

One of many possible causes of chronic kidney disease (CKD) is tubulointerstitial nephritis (TIN). TIN is characterized by inflammation of the tubulointerstitial compartment that potentially leads to progressive loss of kidney function. The majority of TIN cases are caused by drugs, autoimmune diseases, or infections.[1] 5-Amino salicylic acid (5-ASA) is a drug that is commonly used to treat Crohn's disease but may also cause TIN.[2] Importantly, TIN can also cause peculiar tubular dysfunctions including distal renal tubular acidosis (dRTA).[1] One of the pathognomonic features of dRTA is the development of calcium phosphate (CaP) kidney stones.[3] We report a patient experiencing recurrent nephrolithiasis and concomitant CKD where dRTA was caused by a 5-ASA-mediated TIN. Finally, we describe, for the first time, the successful treatment of hypocitraturia with a sodium/glucose cotransporter 2 inhibitor (SGLT2i) with potential clinical implications for patients with dRTA as well as CaP stones.

CASE REPORT

A man in his late 40s was admitted to the outpatient nephrology department in April 2021 because of his reduced estimated glomerular filtration rate (eGFR) (serum creatinine 1.7 mg/dL; eGFR (CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration]) 49 mL/min/1.73 m^2). Further, no specific evaluation of the etiology of his recurrent kidney stone disease had taken place, although >100 stones had already been removed by ureterorenoscopy or extracorporal lithotripsy. Although the patient had only singular kidney stones in 1996 and 2006, formation of concrements had promptly increased since 2018. Kidney stone analyses since 2018 revealed that the stones were composed of CaP. In addition to nephrolithiasis, the patient also had a history of Crohn's disease since 2012 that was being treated with budesonide and 5-ASA (3-4 g/day orally and 1 g/day as a suppository) and showed no signs of activity.

The initial laboratory report in our outpatient department from April 2021 displayed elevated serum creatinine (1.7 mg/dL; eGFR 47 mL/min/1.73 m^2). Elevated serum creatinine was first documented in February 2018 (1.3 mg/dL; eGFR 64 mL/min/1.73 m^2). Additionally, hypokalemia (3.2 mmol/L), hypophosphatemia (0.7 mmol/L), and vitamin D deficiency (11.8 ng/mL) were documented. Blood cell count, blood urea nitrogen, uric acid, calcium, and intact parathyroid hormone levels were normal. Venous blood gas analysis revealed non-anion gap metabolic acidosis (pH 7.23, PCO_2 51.3 mm Hg, HCO_3^- 17.7 mmol/L, base excess −5.6 mmol/L, anion gap 14.3 mmol/L). Urinary pH was 7.0, urinary anion gap was 17.3 mmol/L, and low-grade leukocyturia, microhematuria, and a protein-creatinine ratio of 648 mg/g were detected.

Because of hypokalemia, non-anion gap metabolic acidosis, elevated urinary pH, and the positive urinary anion gap, as well as the history of multiple CaP kidney stones, a dRTA was suspected. A 24-hour urine sample showed suppressed citrate excretion (0.01 mmol/L/m^2) and increased calcium excretion (300 mg/day), supporting the diagnosis of dRTA.[3] To resolve both the etiology of the dRTA and CKD, we performed a kidney biopsy.

Histopathologic findings showed TIN with atrophic tubules, high-grade interstitial fibrosis (>70% of the specimen), and lymphomonocytic infiltrates (Fig 1). No other lesions including glomerular disease were observed.

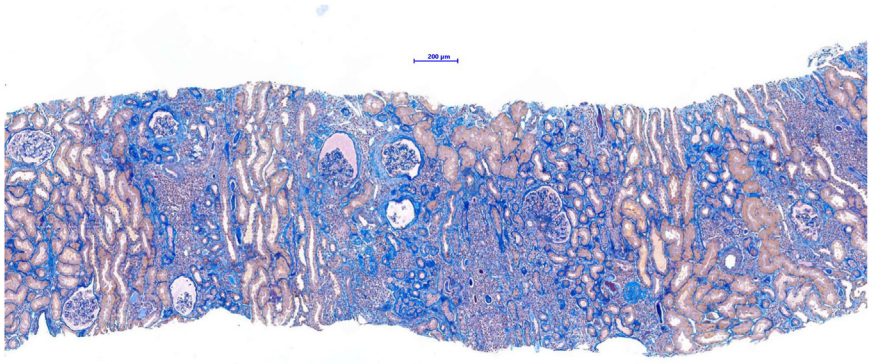

Figure 1. Histopathologic investigation (50×, acid fuchsin orange G [AFOG] stain) showing tubulointerstitial fibrosis and atrophic tubules.

Suspecting drug-related TIN, we stopped 5-ASA and initiated treatment with 75 mg/day prednisolone for 2 weeks with tapering over 5 months. Because of both metabolic acidosis and hypokalemia caused by the dRTA, we initially prescribed 80 mmol/day potassium citrate and further increased the dose to 120 mmol/day. Despite discontinuation of 5-ASA, there was no sign of recurrence of Crohn's disease, and no episodes of diarrhea were documented.

Under this therapy, serum creatinine decreased to 1.4 mg/dL (eGFR 56 mL/min/1.73 m^2) in August 2022. Normal acid-base status and 24-hour excretion of calcium indicated improved tubular function (Table S1). Consequently, the potassium citrate dose was decreased to 40 mmol/day. Although the 24-hour excretion of citrate increased after treatment, citrate excretion was still not normal. Importantly, no newly formed kidney stones were detected.

Because of CKD and a recent study[4] suggesting an increase of citraturia during SGLT2i treatment, 10 mg/day dapagliflozin was started in August 2022. Two months after SGLT2i treatment initiation, citraturia returned to normal. Interestingly, citraturia decreased again when the patient discontinued dapagliflozin treatment on his own in September 2022. However, after restarting dapagliflozin treatment, the 24-hour citraturia again increased (Fig 2). Because of the observed decrease in citraturia after the withdrawal of dapagliflozin and the increase after its reintroduction, the increase in citraturia is plausibly linked to treatment with dapagliflozin (Table S2). During treatment with dapagliflozin, no changes in acid-base status were observed.

DISCUSSION

This case of recurrent CaP nephrolithiasis in Crohn's disease is remarkable for multiple reasons. First, patients with Crohn's disease are usually prone to form calcium oxalate or uric acid stones because of lower urine volume, low urine pH, hypocitraturia, and enteric hyperoxaluria.[5] CaP stones in Crohn's disease are rarely seen because they typically form only in alkalotic urine.[2] Primary hyperparathyroidism, recurrent urinary tract infections, and renal tubular acidosis are the most important causes for CaP stones. We excluded the first 2 possibilities and diagnosed dRTA in our patient. But what is the link between renal tubular acidosis and Crohn's disease?

It is well described in the literature that 5-ASA can provoke TIN by causing direct inflammatory damage in the renal parenchyma or via an idiosyncratic "hypersensitivity reaction."[6] TIN of different causes is associated with syndromes of renal tubular dysfunctions such as dRTA, vasopressin resistance, or Fanconi syndrome.[1] Only 1 case report[7] described dRTA in a patient with Crohn's disease and TIN, also treated with 5-ASA but without kidney stone disease. It is a great challenge to treat patients with 5-ASA-associated TIN. Apart from avoidance of the causative drug, a treatment course with corticosteroids is a therapeutic option with an overall good response.[1] After receiving corticosteroids, however, only 30% of these patients restore their kidney function whereas 10% develop end-stage kidney disease.[6] The high rate of chronic kidney damage and even end-stage kidney disease indicates that 5-ASA may cause severe TIN that can be resistant to anti-inflammatory treatment. In our case, we demonstrated increased GFR after initiating prednisone, effectuating a successful treatment with kidney function improvement.

A novelty in this case report is the notable improvement of citraturia after initiation of dapagliflozin, suggesting SGLT2i as potential treatment option for patients with CaP stones and/or dRTA. SGLT2is are a cornerstone of modern CKD treatment. Interestingly, a clinical trial is currently investigating the potential of SGLT2i to reduce the risk of stone formation by altering the urine composition (SWEETSTONE).[8] Although some studies suggest increased urinary volume because of SGLT2i might decrease kidney stone formation, the exact molecular mechanism of the beneficial effects of SGLT2i on the evolution of kidney stones is still unknown.[9] The main reason for starting therapy with SGLT2i was the study by Harmacek et al,[4] which described an increase in urinary citrate and decrease in urine pH as the possible protective effect of SGLT2i. In our case, we corroborate these data because a striking increase in citraturia after initializing dapagliflozin

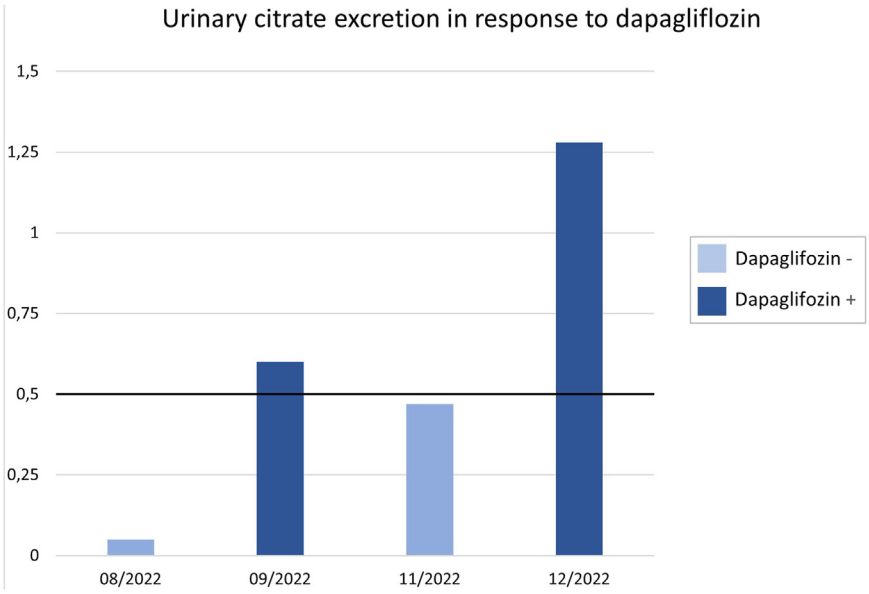

Figure 2. Urinary citrate excretion corrected for body surface area (mmol/L/m^2) in response to dapagliflozin. The lower reference value is indicated by a black line.

was observed, and furthermore, our observation of a reversal of the citraturia-modulating effects of SGLT2i after discontinuation of dapagliflozin indicates biological plausibility. The peculiar effects of SGLT2i on urinary citrate excretion may be a new therapeutic option for patients with urolithiasis as well as dRTA.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Course of laboratory parameters, parameters of venous blood gas analysis and spot urine parameters 24-h urine parameters in relationship to drug dosing.

Table S2: Course 24-h urine parameters in relation to drug dosing.

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