

*Teaching Point*  
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## Chronic hypokalaemia and nephrocalcinosis

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### Introduction

Unravelling chronic hypokalaemia can be a clinical challenge in some patients. History and physical examination can be misleading or inaccurate. Diagnostic steps usually involve assessing urinary potassium excretion, transtubular potassium gradient (TTKG) and concomitant acid–base disturbances. In those patients with low urinary potassium excretion, a gastrointestinal cause for the hypokalaemia would come to mind. In patients with a high urinary potassium excretion, the kidneys themselves are implicated. In any event, acid–base status is extremely helpful and generally indicates which end of the gastrointestinal tract or which level of the nephron is responsible. In patients with high urinary potassium with metabolic alkalosis, the urinary chloride concentration can be particularly helpful in separating surreptitious vomiting from Bartter's syndrome or Gitelman's syndrome. Diuretic abuse may be a confounder; however, metabolic breakdown products and the temporal course of chloride excretion generally solve the mystery. We recently encountered a patient who taxed our diagnostic skills.

### Case report

A 42-year-old woman was first seen in our hospital with 'hyperventilation and panic attacks'. An elevated creatinine concentration (3 mg/dl) and hypokalaemia (3.0 mmol/l) were recorded. A high alcohol intake with complications was suspected but could not be proved. As a child, the patient had been obese and had been sent to a weight loss centre that resulted in a 15 kg weight reduction. She had abused alcohol as an adult and had several earlier admissions for withdrawal and counselling. She also smoked heavily. The patient expressed concern about her weight but denied

bulimia, vomiting induction, laxative or diuretic abuse. She was divorced but lived in a stable relationship.

On examination, she was well kept. The body mass index was 24.7 kg/m<sup>2</sup>, the blood pressure was 130/70 mm Hg and the heart rate was 72 beats/min without orthostatic changes. Her volume status was normal, there was no oedema and the organ systems were intact. She had tooth decay, but no inner enamel loss.

Her creatinine concentration was 1.8 mg/dl, estimated glomerular filtration rate was 33 ml/min and the potassium was 3.3 mmol/l. Her pH was 7.59, PaCO<sub>2</sub> 30 mmHg and HCO<sub>3</sub> 29 mmol/l. The electrolyte values are given in Table 1. Notable are the slightly reduced chloride concentration and the high urine sodium and potassium excretion. The chloride excretion was substantially lower than the cation excretion. The urine anion gap ([UNa-UK]-UCI) was 200 mmol in a 24-h collection. The finding strongly suggests that most of the cation secretion was ingested with some anion other than chloride. The calcium excretion was lower than expected, while the magnesium excretion was normal. The haemoglobin was 11 g/dl; the gamma-glutamyl transferase was slightly elevated at 86 U/l, while other liver enzymes were normal. A urine specimen showed an alkaline pH 8.5. The sediment was bland, and modest proteinuria (368 mg/24 h; albumin 275 mg/24 h, IgG 15 mg/24 h, alpha-1 microglobulin 35 mg/24 h) was present. The renin/aldosterone ratio was 9.4 (normal <50). A 1,25-hydroxyvitamin D level was normal, while the parathyroid hormone concentration was 121 pg/ml (10–65 pg/ml). Urine was tested for diuretic metabolites of furosemide, hydrochlorothiazide, mefruside, piretanide, xipamide and canrenone, but none were found. Renal ultrasound revealed normal-sized kidneys with increased cortical density and a suggestion of nephrocalcinosis. A kidney biopsy revealed normal glomeruli and blood vessels. However, the interstitium showed round cell infiltrate and matrix expansion. Heavy interstitial calcifications were observed in the cortex and outer medulla (Figure 1). Calcifications were also identified in the tubular epithelial cells (Figure 2).

We questioned the patient further and learned that she ravenously ingested citrus fruits (>30 lemons and

**Table 1.** Plasma and 24-h urine electrolyte concentrations

Plasma	Urine
Na <sup>+</sup> : 141 mmol/l (135–148 mmol/l)	Na <sup>+</sup> : 200 mmol/24 h (130–260 mmol/24 h)
K <sup>+</sup> : 3.3 mmol/l (3.7–5 mmol/l)	K <sup>+</sup> : 97 mmol/24 h (65–90 mmol/24 h)
Cl <sup>-</sup> : 94 mmol/l (94–110 mmol/l)	Cl <sup>-</sup> : 97 mmol/24 h (120–240 mmol/24 h)
Ca <sup>2+</sup> : 2.3 mmol/l (2.1–2.6 mmol/l)	Ca <sup>2+</sup> : 0.45 mmol/24 h (<7.5 mmol/24 h)
Mg <sup>2+</sup> : 0.9 mmol/l (0.75–1.05 mmol/l)	Mg <sup>2+</sup> : 4.6 mmol/24 h (1.2–24 mmol/24 h)
Phosphorus: 1.4 mmol/l (0.9–1.4 mmol/l)	Phosphorus: 19 mmol/24 h (<42 mmol/24 h)

grapefruits per week). We measured a 24-h urine oxalate excretion, which was 57 mg/24 h (normal <40 mg/24 h). Six months later, the patient continued to have a creatinine concentration of 2 mg/dl and metabolic alkalosis, although her potassium was normal at 4.2 mmol/l. When off the fruits, her oxalate excretion declined to 28 mg/24 h. Finally, additional insight was obtained from the patient's partner. He was questioned about surreptitious vomiting and reported that he occasionally found the patient in the bathroom under unclear circumstances and had suspected something of that nature. In addition, he reported that the patient regularly used an over-the-counter preparation for 'indigestion' called Kaiser-Natron<sup>®</sup>. A box of the material contains 250 g sodium bicarbonate.

## Discussion

Our patient presented with hypokalaemia, metabolic alkalosis and a normal blood pressure. Her 24-h urinary potassium excretion was high, about twice the daily excretion expected in Germany. Most of the dietary intake of sodium was not in the form of sodium chloride, as twice as much sodium was excreted as compared to chloride. This finding suggests that either the patient ingested other sodium salts (e.g. NaHCO<sub>3</sub>) or that non-renal loss of chloride occurred. Our patient did not report constipation (which might have induced her to ingest excessive alkali) or chronic diarrhoea with persistent (Na or K) chloride losses. Thiazides, metolazone and loop diuretics were absent in her urine. The picture was not consistent with acetazolamide ingestion, since that drug causes metabolic acidosis.

Among all causes of chloride-responsive metabolic alkalosis, surreptitious vomiting seems the most likely. Her history of obesity, her ongoing weight concerns and a serum chloride concentration in the lower normal range might all be in favour of such a suspicion. Further insight was obtained from the partner, who reported regular intake of Kaiser-Natron<sup>®</sup>. This observation explains the remarkable discrepancy between cation and measured anion excretion in the patient's urine. Lowder and Brown reported a patient with metabolic alkalosis, hypokalaemia and hypertension, who was thought to have primary hyperaldosteronism. That patient ingested a box of baking soda (1000 mmol) daily [1].

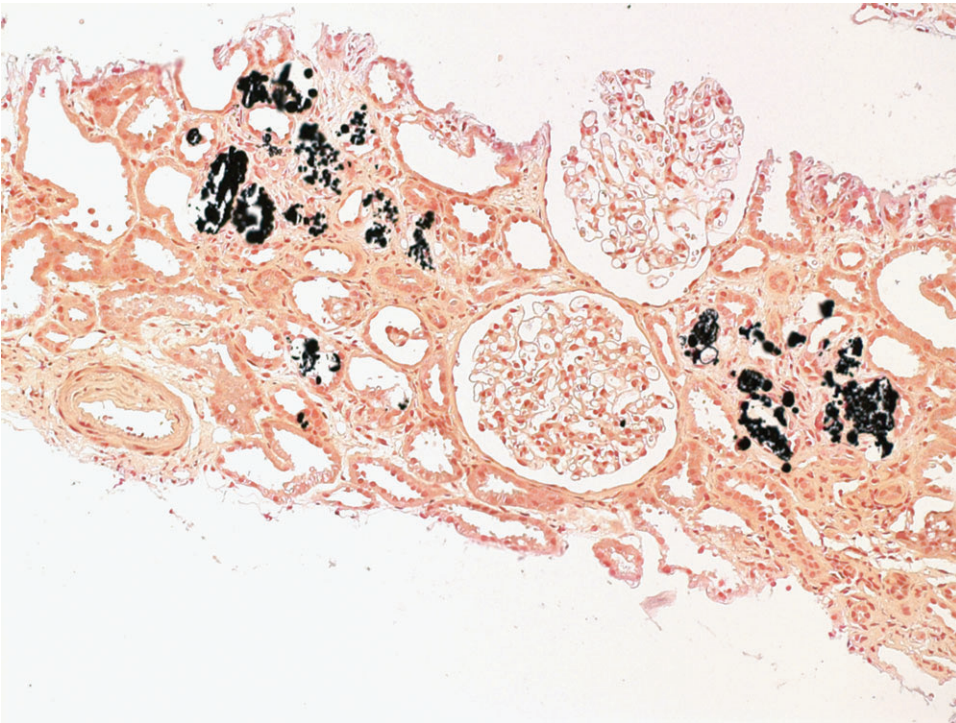
Barter's syndrome could cause nephrocalcinosis, and Gitelman's syndrome is associated with low calcium excretion; however, neither of these diagnoses appeared likely [2]. Blood pressure and the renin-angiotensin system were not disturbed, while the magnesium excretion was normal. We could dismiss conditions causing hypokalaemia and nephrocalcinosis, such as distal renal tubular acidosis, since the patient did not have acidosis.

Persu and colleagues described a young woman with hypokalaemia and metabolic alkalosis who had a similar constellation to what we describe in our patient [3]. Their patient had immune-related potassium-losing interstitial nephritis (IRPLIN) that can also occur in patients with biliary cirrhosis. However, nephrocalcinosis is not a feature of IRPLIN. Our renal biopsy established the presence of interstitial nephritis with nephrocalcinosis. Nephrocalcinosis with hypercalciuria, which our patient did not have, can be caused by hyperparathyroidism or granulomatous diseases, which we were able to exclude. Anatomic genitourinary abnormalities such as medullary sponge kidney were not present on imaging and not consistent with the renal biopsy.

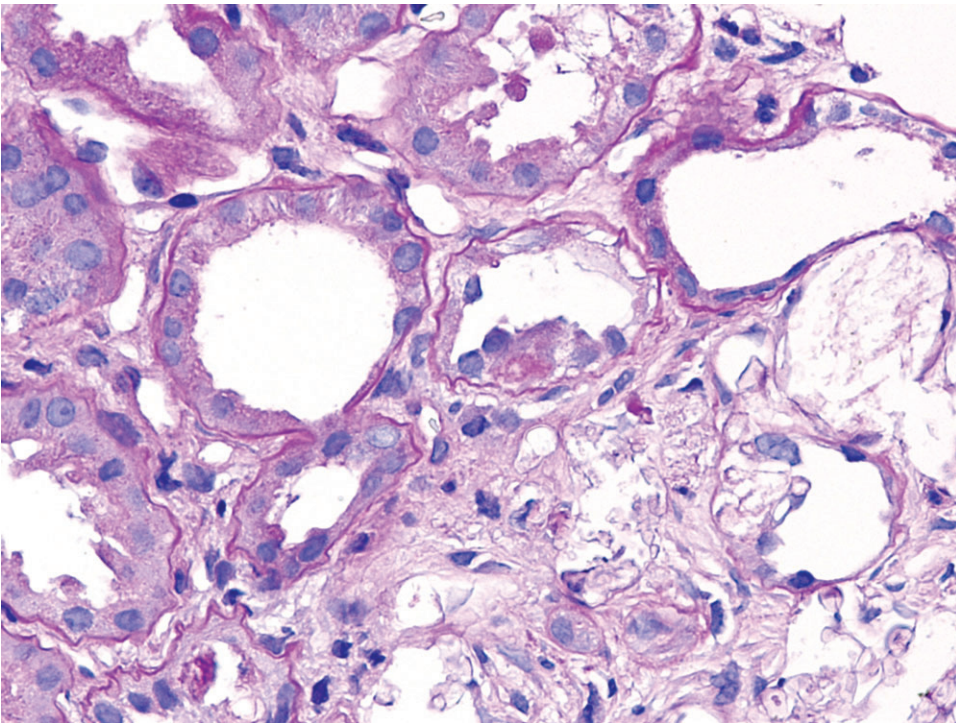
Elevated urinary oxalate levels are another cause of nephrocalcinosis and can result from dietary hyperoxaluria, enteric hyperoxaluria from gastrointestinal disorders or inherited enzyme deficiencies that result in excessive oxalate production. Our data favour dietary hyperoxaluria. Enteric or primary hyperoxaluria usually leads to urinary oxalate values >60–80 mg/24 h. We suggest a relationship between ascorbic acid intake (citrus fruit) and hyperoxaluria. The hyperoxaluria was no longer present when our patient refrained from excessive citrus fruit intake. Nasr *et al.* [4] described a 49-year-old woman with severe tubular and interstitial nephropathy and oxalate deposits with acute renal failure. She admitted ingesting 4 g vitamin C daily along with ibuprofen in generous amounts.

How does oxalate in the medullary collecting duct lead to nephrocalcinosis? Kumar *et al.* [5] recently reported on this issue. The earliest lesion in the kidneys of idiopathic calcium oxalate stone formers is deposition of calcium phosphate in the interstitium, termed a Randall's plaque. The investigators performed studies of crystal transcytosis, cell-mediated calcification and nanoparticles. They focused their attention on the urinary proteins and their influence on adhesion of preformed calcium oxalate crystals to rat continuous inner medullary collecting duct. Their results suggest new paradigms for Randall's plaque formation and idiopathic calcium oxalate stone disease. It seems unlikely that these events are driven solely by physical chemistry; rather, the authors' findings suggest an important influence by specific protein and cellular responses outlined in their paper.

Medications associated with hypokalaemia are necessarily diuretics that inhibit sodium and chloride reabsorption at the thick ascending limb or distal tubule [6]. We are not able to exclude this diagnosis with certainty. Diuretic half-life is brief. Laboratory procedures to determine the drugs or their breakdown products are limited to the time sequence that urine is collected. Furosemide may cause nephrocalcinosis; however, the complication is generally observed in premature infants and not in adults [6].



**Fig. 1.** In the Kossa stain—which is specific for calcium phosphate crystals—many black precipitates can be seen in the cortical interstitium (Kossa, 100 $\times$ ).



**Fig. 2.** Calcium deposits are shown in tubular epithelium and the surrounding interstitium (PAS, 400 $\times$ ).

Calcium phosphate solubility is surely diminished in alkaline urine found in hypokalaemic alkalosis. However, whether or not hypokalaemia can lead directly to nephrocalcinosis and renal insufficiency is a matter of debate. Bock *et al.* described 23 patients who were chronically hypokalaemic for 6.5 years or more because of vomiting induction, diuretics or both [7]. With increasing duration of potassium depletion, renal function deteriorated and two reached end-stage renal disease. Nine patients underwent a renal biopsy, and all had interstitial nephritis [7]. Ogihara *et al.* reported a patient with normotensive normorenaemic primary aldosteronism, persistent hypokalaemia and nephrocalcinosis [8]. This patient also had renal tubular calcifications, while the juxtaglomerular apparatus was normal. Recently, Yasuhara *et al.* reported a patient with bulimia nervosa who developed end-stage kidney disease after 23 years [9]. That patient also had interstitial nephritis, diffuse glomerulosclerosis and proximal tubular swelling. The authors concluded that hypokalaemia played an important role in the long-term progress of renal insufficiency, thus justifying the term ‘chronic kaliopenic nephropathy’.

The connection between chronic hypokalaemia and chronic renal disease remains surprisingly imperfectly defined. Potter *et al.* described such patients who had interstitial nephritis and did not appear to have Bartter’s syndrome [10]. These patients may provide additional genetic clues. Furthermore, despite substantial work, the connection between chronic hypokalaemia and chronic renal disease is not satisfactorily resolved. Meticulous studies by France from almost 50 years ago described the development of periodic acid Schiff-positive granules in medullary epithelial cells and interstitial cells from kidneys of humans and rats with chronic hypokalaemia [11]. His interests in this condition have apparently not been followed by more molecular and ultrastructural studies. Interstitial cellular proliferation was observed in this study. Finally, Riemenschneider *et al.* analysed 40 patients with hypokalaemia and found that at biopsy, the interstitial area was increased with predominantly focal lymphocytic cellular infiltration. GFR impairment correlated with the extent of interstitial fibrosis [12]. These observations would suggest that a well-documented cause of chronic renal failure is receiving little research attention. Perhaps, chronic hypokalaemic nephropathy should be listed as an orphan disease [13].

## Teaching points

- (1) Acquired hypokalaemic metabolic alkalosis is suggestive of diuretic ingestion or gastrointestinal abnormalities such as surreptitious vomiting, chronic diarrhoea or laxative abuse. However, surreptitious bicarbonate ingestion is possible, as was the case here.
- (2) Hypokalaemic nephropathy or kaliopenic nephropathy is a tubulointerstitial disease characterized by polyuria, low-grade proteinuria, development of renal cysts and loss of renal function. Our patient featured nephrocalcinosis, perhaps dependent upon her oxalate ingestion.

*Conflict of interest statement.* None declared.

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