Does hypokalaemia cause nephropathy? an observational study of renal function in patients with Bartter or Gitelman syndrome

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Summary

Background: Hypokalaemic nephropathy has been described in patients with chronic potassium depletion; it is a condition in which proximal tubular vacuolization and interstitial fibrosis occur, resulting in a decline in glomerular filtration rate (GFR) and, in some cases, renal failure. It has been described in patients with chronic diarrhoea, eating disorders, laxative abuse and primary hyperaldosteronism; also occasionally in Bartter syndrome (BS), in which severe hypokalaemia accompanies significant renal sodium and water losses, though rarely in Gitelman syndrome (GS), in which there is equally severe hypokalaemia, but only modest sodium losses.

Aim: We hypothesized that hypokalaemic nephropathy may not be due to potassium depletion per se, but persistently elevated circulating levels of aldosterone, possibly with superimposed episodes of renal hypoperfusion.

Design and methods: We searched UK and European data sets to retrospectively compare serum and urinary parameters in patients with GS and BS.

Results: The patients with GS often had lower serum potassium concentrations than patients with BS, but the BS patients had significantly higher serum creatinine concentrations and lower estimated GFRs (eGFR). BS patients had significantly higher fractional excretions of sodium compared with GS patients, as well as higher plasma renin activities and serum aldosterone levels.

Conclusion: These findings show that in genetically confirmed cases of BS and GS, the degree of hypokalaemia (as an index of chronic potassium depletion) does not correlate with GFR, and that ongoing sodium and water losses, and consequent secondary hyperaldosteronism, may play a more important role in the aetiology of hypokalaemic nephropathy.

Introduction

Potassium depletion can affect renal tubular cell function in several ways: it can impair urinary concentrating ability, in part by decreasing distal nephron responsiveness to vasopressin;¹,² it can increase proximal tubular cell production of ammonia;³ it can increase tubular reabsorption of bicarbonate⁴ and it can increase or decrease tubular sodium reabsorption along the proximal tubule and thick ascending limb, respectively.⁵ Chronic potassium depletion can also cause a form of nephropathy known as hypokalaemic nephropathy, in which hypokalaemia itself is believed to cause a proximal tubular lesion associated with interstitial inflammation and fibrosis, leading to a fall in glomerular filtration rate (GFR).
Conn and Johnson described what they termed ‘kaliopenic nephropathy’ in 1956, after observing renal tubular vacuolation in patients with primary hyperaldosteronism. As they noted at the time, several authors had already described a similar renal lesion in patients with chronic diarrhoeal illnesses, but only one previous author had linked this to hypokalaemia. Further reports followed, although almost all were either in patients with anorexia nervosa, chronic diarrhoea, laxative or purgative abuse or Conn’s syndrome. It is noteworthy that these conditions not only cause hypokalaemia, but they are also associated with increased aldosterone secretion, and most are associated with hypovolaemia due to salt and water loss.

Our own experience of patients with Gitelman syndrome (GS), a monogenic disorder due to abnormalities in the thiazide-sensitive sodium chloride co-transporter (NCC) present in the renal distal convoluted tubule, and in whom hypokalaemia (serum potassium concentration <3 mmol/l) can be striking—although renal sodium and water losses are mild—suggested that impaired renal function occurs rarely, if at all. This is in marked contrast to patients with Bartter syndrome (BS) due to various genetic mutations causing a defect in furosemide-sensitive sodium transport along the thick ascending limb, and in whom significant hypokalaemia also occurs, although with more pronounced renal sodium and water losses, and a tendency to renal impairment.

The renal pathology of hypokalaemic nephropathy has been studied extensively in the potassium-depleted rat, in which there is marked hyperplasia and hypertrophy of tubular cells of the outer medullary-collecting duct, with accumulation of cytoplasmic granules (or droplets). Both principal and intercalated cells undergo hypertrophy, but it is the intercalated cells that hypertrophy the most, especially their luminal surface area, with increases in the length and density of their surface microplicae, and pronounced cytoplasmic granularity. These changes probably represent an adaptive response to increased distal re-absorption of potassium, as the intercalated cell (at least in rodents) has an apical hydrogen potassium adenosine triphosphate-ase (H⁺,K⁺-ATPase) involved in potassium reabsorption. The hypertrophy of these tubular cells may be sufficient to cause obstruction of the tubular lumen and proximal dilatation. Interstitial fibrosis, often with a mononuclear cell infiltrate, is also seen in the setting of prolonged potassium depletion, but the development of this lesion occurs later than the tubular cell changes. Progression to fibrosis is associated with an irreversible decline in GFR.

However, the appearances reported in humans are quite different: although the tubular cells are affected, changes are confined to the proximal tubule, and are degenerative with vacuolization. This pattern occurs in other nephropathies, such as osmotic nephrosis (following intravenous mannitol, volume expanders like dextran and hydroxyethyl starch; contrast dyes, and sucrose-containing immunoglobulin therapy), ethylene glycol intoxication and ciclosporine nephrotoxicity. Late interstitial fibrosis is also a feature in human kidney, but it is usually in the medulla and it may be associated with a mononuclear cell infiltrate. Renal cysts have also been reported to develop in patients with Conn’s syndrome and chronic potassium depletion, and to regress after adrenalectomy. The association with renal cysts has not been observed in other hypokalaemic conditions; moreover, the tubular dilatation seen in the rat model is absent in humans.

In our own clinical experience, patients with BS seem more likely to have or develop chronic renal impairment and a reduced GFR with or without proteinuria, while patients with GS, in whom hypokalaemia can be just as severe, do not have renal impairment. If our clinical impression is correct, then it is difficult to attribute any observed renal impairment to hypokalaemia alone, inviting the question what causes ‘hypokalaemic nephropathy’?

### Methods

Anonymized patient data were pooled from our own UCL Centre for Nephrology database and the larger Hopital Européen Georges Pompidou database. Laboratory and clinical data were available for 113 GS (87 genotyped) and 13 BS (11 genotyped) patients. Estimated GFR was calculated using the modified Modification of Diet in Renal Disease Study Group (MDRD) formula. Data were analysed using GraphPad software, and significance was calculated using the parametric student’s t-test and non-parametric Mann–Whitney test, as appropriate; data are presented as mean and standard error.

### Results

The demographic data on these patients are summarized in Table 1. GS patients were significantly older than BS patients (37.6 ± 1 vs. 29.7 ± 2 years, P=0.04).

No biopsy material was available from any of the genotyped patients.

Serum potassium concentration was lower in GS compared with BS (2.8 ± 0.1 vs. 3.2 ± 0.2 mmol/l,
P = 0.009), serum sodium concentration (139 ± 0.2 vs. 140 ± 1.3 mmol/l, ns) was not significantly different between GS and BS patients (Figure 1).

Total dose of replacement potassium was not significantly different between the GS and BS patients: 7025 ± 1486 vs. 6928 ± 1096 mg/day, ns.

There was no significant difference in serum bicarbonate concentration between GS and BS patients: 30.3 ± 0.5 vs. 31.3 ± 1 mmol/l, ns.

As expected, serum magnesium concentration was significantly lower in GS patients compared with BS patients: 0.6 ± 0.01 vs. 0.8 ± 0.04 mmol/l, P < 0.0001.

Serum creatinine concentration was significantly higher in BS compared with GS patients: 144 ± 22 vs. 72 ± 1.6 µmol/l, P < 0.0001; the estimated GFRs (eGFR) were significantly lower in BS compared with GS patients: 60.3 ± 7 vs. 100 ± 2 ml/min/1.73 m², P < 0.0001 (Figure 2).

In keeping with the increased renal losses of sodium in BS, the fractional excretion of sodium (FENa) was significantly higher in BS compared with GS patients: 1.29 ± 0.25 vs. 0.911 ± 0.04%, P < 0.0001 (Figure 3). However, there was no significant difference in the recorded blood pressures of GS and BS patients: systolic BP 119 ± 2.9 vs. 118 ± 7.4 mmHg, ns; diastolic BP 74.5 ± 2.2 vs. 68.9 ± 3.7 mmHg, ns (Figure 4).

As reported previously,27 plasma renin concentration was lower in GS compared with BS patients: 145 ± 14.5 vs. 624 ± 259 mU/l, P < 0.0001; as was plasma aldosterone concentration: 360 ± 48.3 vs. 2442 ± 1076 pmol/l, P < 0.0001 (Figure 5).

Although there was a tendency towards more proteinuria in BS compared with GS patients (0.28 ± 0.07 vs. 0.14 ± 0.02 g/l, ns), this was not...
statistically significant; overall, proteinuria was so small that urinary protein/creatinine ratios could not be calculated reliably.

Serum parathyroid hormone concentrations were not significantly different between GS and BS patients: 19.4±1.5 vs. 23.3±1.5 pg/ml, ns. (There was no significant correlation between serum PTH and magnesium concentrations.)

Pearson correlation analysis did not support an association of hypokalaemia with worsening renal function; serum potassium and eGFR had an inverse correlation \((r=-0.24, r^2=0.06, P=0.007)\), serum potassium and serum creatinine had a positive correlation \((r=0.23, r^2=0.05, P=0.007)\). Plasma renin concentration had a positive correlation with serum creatinine \((r=0.385, r^2=0.15, P=0.0001)\), serum aldosterone had a strong positive correlation with serum creatinine \((r=0.462, r^2=0.21, P<0.0001)\), consistent with renin–angiotensin–aldosterone system (RAAS) activation and/or hypovolaemia contributing to a decline in renal function.

**Discussion**

These data show differences in renal function between GS and BS patients: the latter showing variable reductions in eGFR, while the former have preserved renal function. However, BS often has a more overt phenotype with marked sodium and water losses, usually presenting in infancy and typically with severe hypovolaemia; the earlier age at presentation also explains the age difference observed between the two groups. Hypercalciuria is also a feature of BS, particularly in types 1 and 2, and can be associated with nephrocalcinosis, which might be expected to contribute to renal impairment; however, in distal renal tubular acidosis (dRTA), in which nephrocalcinosis is a more consistent finding, as well as in medullary sponge kidney, a reduced GFR (in the absence of a history of renal stone complications) is unusual.²⁸

Although defective urinary concentrating ability may occur in renal impairment, there was no correlation between eGFR and FE\(_{\text{Na}}\) in the BS patients (data not shown); the greater tendency of BS toward salt and water loss is well described. This tendency for BS patients to lose more sodium is also reflected in greater stimulation of the RAAS. Indeed, in the light of no observable difference in the mean serum potassium concentrations could this low volume, high renin, high aldosterone state in BS be a more important determinant of any renal impairment, and thus of ‘hypokalaemic nephropathy’?

The reported cases of hypokalaemic nephropathy were chiefly in patients with diarrhoeal disease, anorexia nervosa, or primary hyperaldosteronism. This raises the possibility that the interstitial fibrosis is caused by tissue exposure to high levels of aldosterone, either alone or in association with recurrent hypovolaemic insults (similar to those that cause the renal impairment seen in familial dysautonomia²⁹).

Patients with chronic diarrhoea³⁰,³¹ or anorexia and bulimia³²,³³ have high renin and aldosterone levels, and the concept of hypokalaemic nephropathy was initially raised in patients with primary hyperaldosteronism (in whom volume contraction is not a feature). In addition, there is reason to suspect that the rat model of hypokalaemia may actually be a model of secondary hyperaldosteronism: rats fed a low potassium diet are anorectic,³⁴–³⁶ growth retarded,³⁴ and hypotensive.³⁵,³⁷,³⁸ While information on aldosterone activation in these animals is lacking in the published literature, they are known to have high plasma renin and angiotensin levels.³⁷

In other human diseases characterized by hypokalaemia, but without RAAS stimulation or hypotension, such as dRTA (see above) and Liddle syndrome (suppressed aldosterone with hypertension), there are no reports of renal biopsies showing the features of hypokalaemic nephropathy, and the few reports of cystic appearances on renal imaging have been in association with nephrocalcinosis.³⁸,⁴⁰ The syndrome of apparent mineralocorticoid excess (AME) is another example that potentially dissociates aldosterone levels from hypokalaemia, but in AME, unlike in Liddle syndrome, there is cortisol-dependent mineralocorticoid receptor stimulation; unfortunately, there is again a lack of biopsy data and the radiological appearances of cysts are seen only with nephrocalcinosis.⁴¹

The pro-fibrotic effects of aldosterone are well known in the myocardium, but aldosterone also induces renal fibrosis in hypertensive rats.⁴²

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**Figure 5.** This shows the mean serum renin and aldosterone concentration in GS and BS patients. The asterisks denote statistical significance \((P<0.001)\).
Angiotensin II is also pro-fibrotic, and induces the expression of transforming growth factor-β (TGF-β) and renal fibrosis in rats; it can also act as a pro-inflammatory cytokine (see reference for a review). Moreover, renin itself may cause fibrosis: binding of renin to the (pro)renin receptor has been shown to provoke phosphorylation of MAP kinases that upregulate the expression of pro-fibrotic molecules such as TGF-β, Plasminogen activator inhibitor-1 (PAI-1), collagen 1 and fibronectin. These molecules, independent of angiotensin II, lead to increased fibrosis, and this may be why (like anti-aldosterone therapy) the renin antagonist aliskiren can attenuate renal fibrosis in a rat model of diabetic nephropathy.

Could aldosterone mediate the prominent vacuolization seen in the proximal tubular epithelium? Aldosterone is usually thought to act on the distal convoluted tubule and collecting duct, but a direct effect increasing sodium absorption in the proximal tubule was described 40 years ago. This effect is due to the activation of the apical sodium-proton exchanger NHE3, which probably occurs through trafficking of cytoplasmic preformed NHE3, rather than any increase in its transcription, since total NHE3 expression is not increased following aldosterone stimulation, unlike apical NHE3 activity.

The distinctive distal tubular changes of intercalated cell hypertrophy seen in hypokalaemic animal models seem to be absent in humans, but the explanation for this is unclear. One speculation is that these changes may be related to compensatory activity of the intercalated cell’s H+,K+-ATPase, which is a reabsorptive mechanism for potassium. This exchanger is similar to that found in the gastric mucosa, and is expressed in rabbit and rat intercalated cells, but it has very sparse expression in the human kidney.

In conclusion, we propose that the phenomenon of ‘hypokalaemic nephropathy’ is not due to hypokalaemia itself, but is perhaps the result a direct effect of aldosterone on the proximal tubular epithelium, and later the renal interstitium. In addition, we suspect that fluctuations in circulating volume and exacerbations of hypovolaemia are likely to occur in many conditions linking hypokalaemia with renal impairment. However, although we do not think the association with hypokalaemia is a direct one, we acknowledge that patients with BS are more likely than GS patients to have received early and longer-term non-steroidal anti-inflammatory therapy (NSAID), usually as indomethacin; this might be an additional factor in any renal impairment.

Finally, our data show preserved renal function in GS patients, in contrast to BS patients with similar levels of hypokalaemia, which is consistent with our view that hyperaldosteronism, with or without fluctuating hypovolaemia, is a more likely cause of any associated renal impairment. If we are correct, then long-term blockade of the mineralocorticoid receptor in BS with spironolactone or eplerenone (or perhaps even by direct renin inhibition) may be justified more for renal protection than for trying to correct hypokalaemia per se, which can rarely be achieved.

Conflict of interest: None declared.

References


