



Hypokalaemia: common things occur commonly – a retrospective survey

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DECLARATION

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None declared

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Guarantor

CI

Contributorship

CI had the idea, GJ ran the enquiry, AR extracted data from casesheets, CI wrote the first draft, all authors contributed to the final draft

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Reviewer

David Goldsmith

Summary

Objectives To define the causes of hypokalaemia in an unselected adult population.

Design Retrospective survey of biochemistry database.

Setting District general hospital in southwest Scotland.

Participants and main outcome measures There were 187,704 measurements of urea and electrolytes in 2010. Sixty-one patients had serum potassium <2.5 mmol/L on at least one occasion.

Results Average age of the patients was 71 (range 33–99) years. The most common causes were diarrhoea and/or vomiting (51% of cases), diuretic therapy (47%), nutritional causes including poor dietary intake, re-feeding syndrome and inadequate potassium supplementation when patients were nil by mouth (37%). In 25% of patients a transient and profound fall in serum potassium appeared to coincide with their acute illness. Acute alcohol intoxication and/or alcohol withdrawal were prominent features in 11% of patients. More than one cause was commonly present. There were no cases of Bartter's, Gitelman's or Liddle's syndromes or of hypokalaemic periodic paralysis in this study.

Conclusions Severe hypokalaemia <2.5 mmol/L occurs at least once a week in a district general hospital with a catchment population of around 150,000, suggesting there may be around 300 cases a week in the UK (population around 50,000,000). Diuretics, vomiting and diarrhoea are commonly implicated as are nutritional causes, acute illness and alcohol. Bartter's, Gitelman's, Liddle's syndrome and hypokalaemic period paralysis are all extremely uncommon.

Introduction

Hypokalaemia is a common biochemical abnormality made complex by difficult physiology, an over-emphasis on rare syndromes and by algorithms that are not always easy to follow. The bewildering number of pumps and channels shown in

student textbooks hardly serve to demystify the subject (Figure 1),¹ while the lists of causes of hypokalaemia fail to distinguish between those that might be encountered once a week, e.g. vomiting and those that might be experienced once in a professional lifetime, e.g. Gitelman's syndrome.² The over-emphasis on rare syndromes

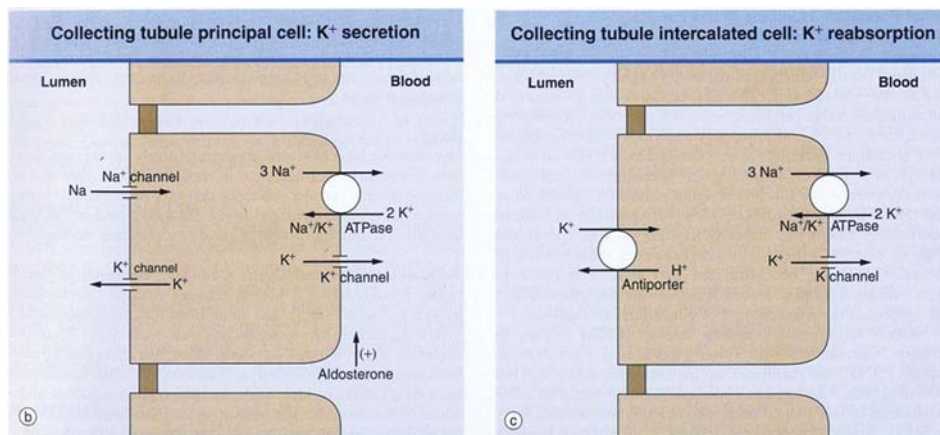
Figure 1**Mechanisms of potassium re-absorption and secretion in the principal cell and intercalated cell of the cortical collecting duct (Source: Kumar and Clark 2010)**

Figure 9.5 A–C, Mechanisms of potassium reabsorption and secretion in the thick ascending limb and the collecting tubule principal and intercalated cells.

is perpetuated by the Member of Royal Collage of Physicians (MRCP) exam in which a candidate is expected to know as much about Bartter's syndrome as the mechanisms of hypokalaemia associated with diuretic therapy. Flow charts for the evaluation of hypokalaemia are often unhelpful: in a recent algorithm, measurement of urine potassium:creatinine ratio (KCR), blood pressure, extracellular fluid volume status, serum bicarbonate and urinary chloride appear to be required before concluding that the cause of hypokalaemia might be vomiting.³

Methods

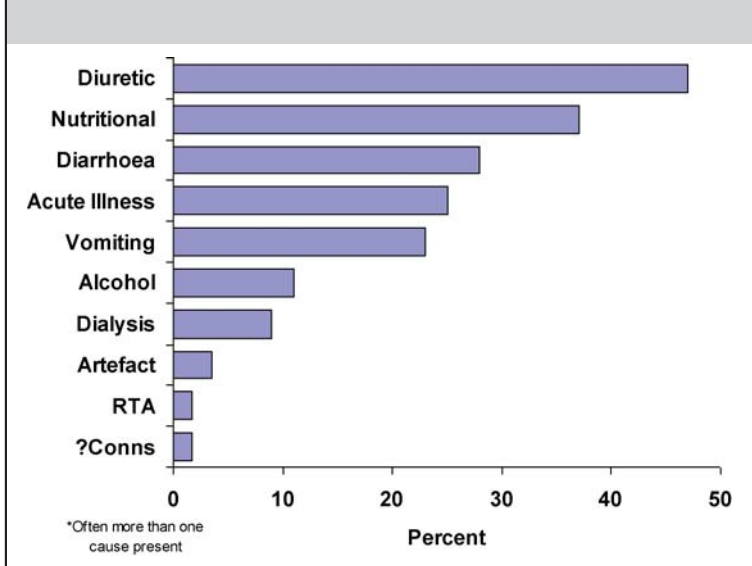
Against this background and in order to put the causes of severe hypokalaemia into a more recognizable clinical context, we undertook a survey of all patients in southwest Scotland (population 147,000) whose serum potassium was less than 2.5 mmol/L during the course of one year between 1 January 2010 and 31 December 2010. Casesheet review was undertaken in every case. We interrogated the lab browser to determine the number of patients with severe hypokalaemia who also had measurements of serum bicarbonate, serum chloride, serum magnesium, serum phosphate, together with any measurement of urine potassium and the time between presentation with severe hypokalaemia and that

measurement. We also undertook a survey of the discharge codes of all patients who had been admitted to Dumfries and Galloway Royal Infirmary between 1 January 2007 and 30 June 2011. Gitelman's syndrome and Liddle's syndrome did not have diagnostic codes and so it was not possible to assess the prevalence of these diagnoses by this method. We were however able to test for 'Bartter's syndrome and any other hyperaldosteronism' (Code E268) and hypokalaemic periodic paralysis (HPP) (Code G723).

Results

There were 187,704 measurements of urea and electrolytes during a period of one year. Sixty-one patients had serum potassium <2.5 mmol/L on at least one occasion. The average age of the patients with hypokalaemia of this severity was 71 (range 33–99) years. Forty-one (67%) patients were women. Only four patients with hypokalaemia were managed exclusively in primary care. Of the remaining 57, 23 (38%) had serum potassium <2.5 mmol/L on admission, while 34 (56%) developed severe hypokalaemia during their hospital stay. Serum bicarbonate was measured in 49 (86%), serum phosphate in 23 (40%) and serum magnesium in 29 (51%). Only six (11%) patients had a measurement of urine potassium and only

Figure 2
Causes of severe hypokalaemia in southwest Scotland 2010



two of these (4% of the secondary care patients) had a urine KCR within 24 h of admission.

The likely causes of hypokalaemia are shown in Figure 2. Percentages in Figure 2 do not add up to 100% because more than one cause was commonly present. Diarrhoea and/or vomiting were associated with severe hypokalaemia in 51% (29/57) of cases. Diuretic therapy was likely to have contributed to or was solely responsible for severe hypokalaemia in 47% of cases. Nutritional causes including poor dietary intake, re-feeding syndrome and inadequate potassium supplementation when patients were nil by mouth, were the next most likely contributors to hypokalaemia in 37% cases. In 25% of patients a transient and profound fall in serum potassium appeared to coincide with their acute illness. Often both were present. Acute alcohol intoxication and/or alcohol withdrawal were prominent features in 11% of patients with severe hypokalaemia. Serum potassium fell below 2.5 mmol/L in five patients after dialysis. Artefact accounted for two of the patients in this series: one who had blood taken from a drip arm and another during a massive blood transfusion. One patient had renal tubular acidosis and one patient with hypertension and hypokalaemia probably had primary hyperaldosteronism but declined further investigations. There were no cases of Bartter's

syndrome, Gitelman's syndrome, Liddle's syndrome or HPP in this study.

Our survey of discharge codes of all patients admitted to Dumfries Infirmary over a four-year period showed that 64,418 patients had been admitted on 148,384 occasions during this time. There were five codes for Bartter's syndrome and any other hyperaldosteronism, and no codes for HPP. When we checked the discharge summaries of the patients coded E268, we found that only 2/5 actually had Bartter's syndrome and that neither were new diagnoses.

Discussion

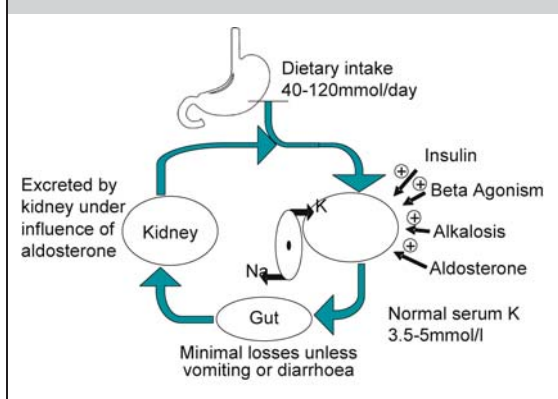
The main findings of our study are firstly, that severe hypokalaemia <2.5 mmol/L occurs at least once a week in a district general hospital with a catchment population of around 150,000; and secondly, that diuretics, vomiting and diarrhoea are commonly implicated as are nutritional causes, acute illness and alcohol. There were no cases of Bartter's syndrome, Gitelman's syndrome, Liddle's syndrome or HPP, and no new cases of Bartter's syndrome or HPP in a four-year review of all patients admitted to our hospital. These results suggest that common things occur commonly and that the causes of severe hypokalaemia are usually fairly obvious.

The main strength of our study is that there were no missing data, which means that our results are likely to be representative of the causes of hypokalaemia in an unselected adult population. Our main limitation is that not all patients had all tests, in particular a reliable measure of urine potassium. We will argue later that as the causes of severe hypokalaemia are usually fairly obvious, this may not always be necessary.

Regulation of serum potassium

An understanding of the regulation of serum potassium provides a convenient framework for classifying the causes of hypokalaemia.⁴ Dietary intake of potassium is generally of the order 40–120 mmol per day. Sodium-potassium-ATPase pumps in the cell walls of skeletal muscle ensure that 98% of total body potassium is intracellular and only 2% extracellular.⁵ With total body potassium of approximately 3600 mmol, this must

Figure 3
Overview of potassium homeostasis



mean that only 65 mmol potassium is extracellular and neatly explains why even small transcellular shifts of potassium can lead to significant changes up or down in serum potassium.³ Insulin, beta adrenergic stimulation, alkalosis and aldosterone are all known to activate the sodium potassium ATPase pump, pushing potassium into muscle cells (Figure 3).

The gut is associated with minimal losses of potassium unless there is vomiting or diarrhoea (see later), leaving the kidney mainly responsible for excretion of potassium on a day-to-day basis. The mechanisms by which the kidney regulates potassium are undeniably complex. Nearly all fil-

tered potassium is re-absorbed by the proximal nephron. This occurs passively with sodium in the proximal tubule and actively with sodium and chloride in the thick ascending limb of the Loop of Henle. Nearly all urinary potassium is secreted as a result of the actions of two important cells in the cortical collecting duct. The principal cell, which is activated by aldosterone and distal tubular sodium delivery, secretes potassium in exchange for sodium. The intercalated cell, which is activated by hypokalaemia and acidosis, re-absorbs potassium in exchange for hydrogen. The net effect of these two cells is usually potassium secretion (Figure 4).

Causes of hypokalaemia

Using this framework, causes of hypokalaemia may be classified as relating to intake, transcellular shifts, gut and renal losses (Figure 5). Nutritional causes, including inadequate dietary intake and inadequate intravenous potassium replacement in patients who are nil by mouth, commonly contribute to hypokalaemia. Even small transcellular shifts can lead to significant hypokalaemia, and this may be one of the reasons as to why hypokalaemia occurs frequently in re-feeding syndrome⁶ and in patients who become acutely ill.⁷

Vomiting and diarrhoea are important causes of hypokalaemia although the mechanisms

Figure 4
Potassium regulation by the proximal and distal nephron of the kidney

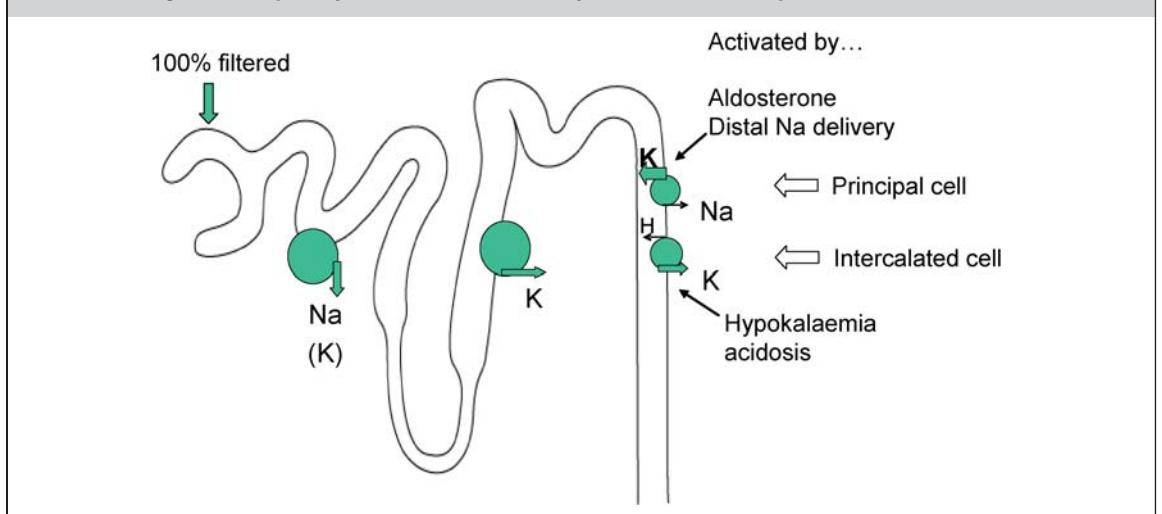
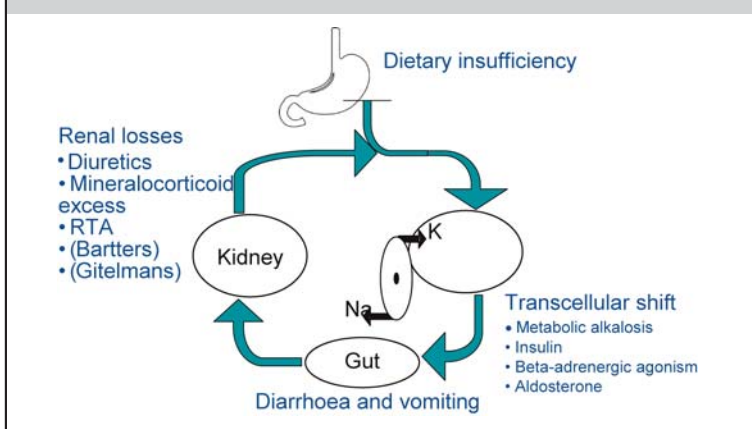


Figure 5
Causes of hypokalaemia



differ. Vomit contains mainly acid, with very little potassium (5–10 mmol/L). Loss of acid leads to alkalosis which pushes potassium into the cells. Loss of volume leads to aldosterone release with renal potassium wasting. Vomiting therefore causes hypokalaemia with metabolic alkalosis and, usually, renal potassium wasting (Figure 6). Diarrhoea, in contrast, contains considerable quantities of potassium (30–60 mmol/L) and bicarbonate. The body strives for electro-neutrality and retains chloride to compensate for the loss of bicarbonate and as such, the patient with diarrhoea commonly presents with hypokalaemia and hyperchloraemic metabolic acidosis (Figure 6).

The kidneys are primarily responsible for eliminating potassium from the body and it should come as no surprise therefore to learn that many causes of hypokalaemia are renal in origin. The commonest renal cause of hypokalaemia is diuretic therapy, particularly when loop diuretics and thiazides are co-prescribed.⁸ Loop diuretics block the sodium-potassium-chloride co-transporter in the thick ascending limb of the Loop of Henle, while thiazides block the sodium-chloride co-transporter in the distal convoluted tubule (Figure 7). The main consequence of blocking these pumps at these sites is increased sodium delivery to the principal cells of the cortical collecting duct, which avidly retain sodium in exchange for potassium. The intercalated cell responds to the resulting hypokalaemia by exchanging potassium for hydrogen to give the characteristic hypokalaemic metabolic alkalosis of diuretic therapy.

Figure 6
Mechanism of hypokalaemia in diarrhoea and vomiting

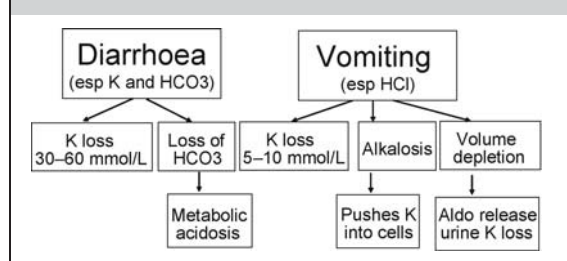
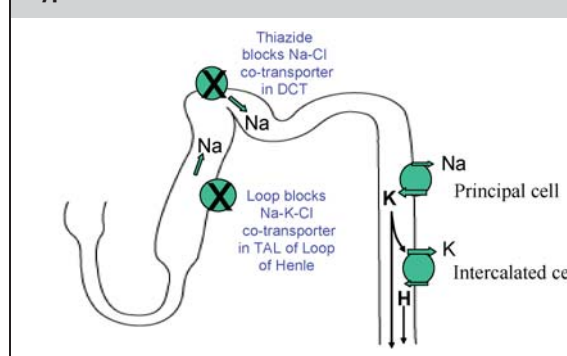


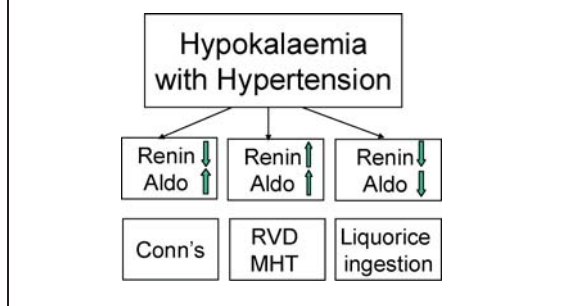
Figure 7
Importance of serum bicarbonate in evaluation of hypokalaemia



The other causes of renal potassium wasting, while undoubtedly important, are much less common. They include proximal (type 2) and distal (type 1) renal tubular acidosis. Distal RTA is the more common of the two and has numerous causes. The clue to diagnosis is hypokalaemic hyperchloraemic metabolic acidosis with failure to acidify the urine. There are three syndromes of mineralocorticoid excess.⁹ These are primary hyperaldosteronism, secondary hyperaldosteronism and prolonged ingestion of liquorice. The clue to these diagnoses is that of hypertension with hypokalaemia without other obvious cause. Measurements of plasma renin and aldosterone are often required to make a diagnosis (Figure 8).

This leaves the rare syndromes. HPP is an autosomal-dominant disorder associated with mutations in genes that control the movement of potassium into muscle cells. HPP causes episodes of extreme muscle weakness typically beginning in childhood or adolescence.¹⁰ Liddle's syndrome

Figure 8
Mechanism of hypokalaemia with diuretic therapy



is an autosomal-dominant disorder affecting epithelial sodium channels in the cortical collecting duct causing apparent mineralocorticoid excess. Detailed descriptions of Bartter's and Gitelman's syndromes can be found elsewhere.^{11,12} An aide-memoire for the generalist is that Bartter's syndrome mimics the action of a loop diuretic and Gitelman's syndrome the action of a thiazide. It is likely that most of us will go through our professional careers without seeing a new case.

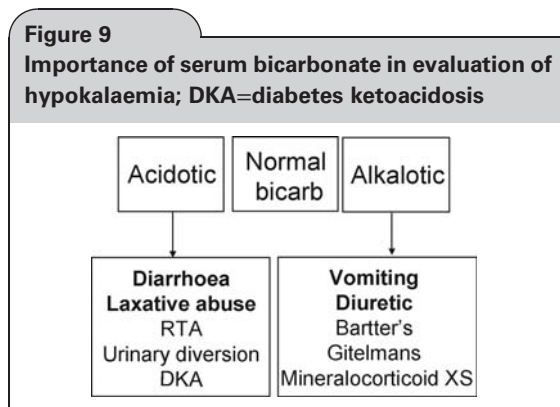
Investigations that might help determine the cause

Even though the cause of hypokalaemia is likely to be obvious in most cases, a limited biochemical screen is likely to be helpful. Serum bicarbonate is probably the single most useful additional test (Figure 9). Hypokalaemia associated with diuretic therapy or vomiting usually causes a metabolic alkalosis as do Bartter's syndrome, Gitelman's syndrome and mineralocorticoid excess. Hypokalaemia associated with diarrhoea is frequently associated with hyperchloraemic (normal anion gap) metabolic acidosis. Other causes of a hypokalaemic hyperchloraemic metabolic acidosis are an ileal conduit, acetazolamide and renal tubular acidosis (diagnoses should be obvious). Laxative abuse and villous adenoma of colon may both present with unexplained hypokalaemia. Here the potassium loss is chronic rather than acute. Some of these patients may present with alkalosis rather than acidosis.¹³ Patients with diabetic keto-acidosis tend to have a total body potassium deficit but may be hyperkalaemic, normokalaemic

or hypokalaemic on presentation. Again the diagnosis will usually be obvious.

Serum magnesium and serum phosphate may also add useful information. Hypomagnesaemia is present in up to 40% of patients with hypokalaemia.¹⁴ It commonly coexists because magnesium is lost with potassium in diarrhoea and with diuretic therapy. Hypomagnesaemia may also lead to urinary potassium loss by an uncertain mechanism. It is commonly associated with alcoholism as a consequence of diarrhoea and poor nutritional intake.¹⁵ A particular reason for measuring serum magnesium in a patient with hypokalaemia is that it may be difficult to correct the hypokalaemia unless or until the hypomagnesaemia is also corrected. Measurement of serum phosphate may also help determine the cause of hypokalaemia when that cause is not obvious. Hypophosphataemia may indicate poor nutrition, particularly when patients begin to eat again after a period of starvation or poor intake.⁶ The reason for this is that during periods of starvation the body starts burning fat and protein. Re-introduction of carbohydrate leads to a surge of insulin which drives both potassium and phosphate into cells.⁶

Some measure of urine potassium excretion is usually recommended in the evaluation of hypokalaemia although if the cause is obvious, this is unlikely to be a necessary test. A difficulty here is obtaining a urine sample before replacement therapy is started. A spot urine potassium in mmol/L takes no account of urinary concentration and should be discouraged for the same reasons that led us to abandon urine dipstick (a semiquantitative measure of urine albumin in g/L) in favour of urine albumin:creatinine ratio and protein:creatinine ratio. Twenty-four hour urine potassium must presumably go the same way as 24 h urine protein, i.e. be abandoned because it is cumbersome, messy and frequently incomplete. It is, moreover, unrealistic to undertake a 24 h urine collection before starting replacement therapy in a patient whose serum potassium is less than 2.5 mmol/L. Urine KCR would appear to avoid these pitfalls and is currently recommended. Urine KCR >2.5 is said to indicate renal potassium wasting,¹⁶ though some authorities use the lower cut-off point of 1.5.^{17,3} Two other more complex measures of renal potassium output, transtubular potassium gradient and fractional excretion of



potassium, have low added value in the assessment of hypokalaemia.³

Finally, mention must be made of plasma renin and aldosterone as tests that might occasionally be useful in the diagnosis of hypokalaemia (Figure 8). The indication for such measurement should really be limited to patients with hypertension and hypokalaemia for which there is no other obvious explanation.⁹ Plasma renin and aldosterone define three hypertensive scenarios, the commonest of which is probably primary hyperaldosteronism (Figure 9). Forty percent of hypertensive patients with low renin and high aldosterone will have an aldosterone secreting adrenal adenoma (Conn's syndrome), with most of the remainder having bilateral adrenal hyperplasia. Confirmation of a Conn's adenoma requires, additionally, that a patient undergo adrenal computed tomography scan and adrenal vein sampling. Around 20–40% of patients with Conn's syndrome will have their hypertension cured or significantly improved by adrenalectomy.¹⁸ Diagnoses of renovascular disease and malignant hypertension are usually established without measuring plasma renin and aldosterone. Inappropriately low plasma renin and aldosterone suggest suppression by an unmeasured mineralocorticoid, such as liquorice.¹⁹

Summary

Severe hypokalaemia <2.5 mmol/L occurs at least once a week in a district general hospital with a catchment population of around 150,000, suggesting there may be around 30 cases per week in Scotland (population around 5 million).

Diuretics, vomiting and diarrhoea are commonly implicated, as are nutritional causes including re-feeding, acute illness and alcohol. Measurement of serum bicarbonate, chloride, phosphate and magnesium may help in diagnosis. Our experience suggests that urine potassium is not always measured and not always necessary, though review of the literature suggests that urine KCR is probably the most useful measure of urine potassium loss when the diagnosis of hypokalaemia is not obvious. Bartter's, Gitelman's, Liddle's syndrome and HPP are all extremely uncommon.

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