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Original Article

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Hypokalaemia and subsequent hyperkalaemia in hospitalized patients

Meindert J. Crop[1], Ewout J. Hoorn[1], Jan Lindemans[2] and Robert Zietse[1]

[1]Department of Internal Medicine and [2]Department of Clinical Chemistry, Erasmus Medical Center, Rotterdam, The Netherlands

Abstract

Background. The objective was to study the epidemiology of hypokalaemia [serum potassium concentration (S_K) <3.5 mmol/l] in a general hospital population, specifically focusing on how often and why patients develop subsequent hyperkalaemia ($S_K \geq 5.0$ mmol/l).
Methods. In a 3-month hospital-wide study we analysed factors contributing to hypokalaemia and subsequent hyperkalaemia.
Results. From 1178 patients in whom S_K was measured, 140 patients (12%) with hypokalaemia were identified (S_K 3.0 ± 0.3 mmol/l). One hundred patients (71%) had hospital-acquired hypokalaemia. Common causes of hypokalaemia included gastrointestinal losses (67%), diuretics (36%) and haematological malignancies (9%). In 104 patients (74%), hypokalaemia was multifactorial. Hypokalaemia frequently coexisted with hyponatraemia (24%) and, when measured, hypomagnesaemia (61%). Twenty-three patients (16%) developed hyperkalaemia (highest S_K 5.7 ± 0.7 mmol/l) following hypokalaemia. In these patients, potassium suppletion was not more common (70 *vs* 59%, $P = 0.5$), but when potassium was given, the total amount administered was significantly higher (median 350 mmol *vs* 180 mmol, $P = 0.02$). Furthermore, these patients more often received total parenteral nutrition (17 *vs* 4%, $P = 0.02$) and magnesium suppletion (30 *vs* 9%, $P = 0.009$), and more often had haematological malignancies (22 *vs* 6%, $P = 0.03$).
Conclusions. Hypokalaemia is a multifactorial and usually hospital-acquired condition associated with hyponatraemia and hypomagnesaemia. One out of every six patients with hypokalaemia developed subsequent hyperkalaemia. Besides potassium suppletion, total parenteral nutrition (source of potassium), magnesium suppletion (may reduce kaliuresis) and haematological malignancy (may cause cell lysis) contribute to hyperkalaemia following hypokalaemia. Caution with potassium suppletion and frequent monitoring of S_K may prevent iatrogenic hyperkalaemia.

Keywords: haematological malignancy; hypomagnesaemia; hyponatraemia; magnesium suppletion; potassium suppletion; total parenteral nutrition

Introduction

Hypokalaemia, defined as a serum potassium (S_K) concentration <3.5 mmol/l, is a common and potentially serious electrolyte disorder [1,2]. The estimated incidence of hypokalaemia in hospitalized patients is 20%, while the incidence of severe hypokalaemia, defined as <3.0 mmol/l, is approximately 5% [3]. Causes of hypokalaemia can be divided in either true potassium depletion, mostly caused by renal or gastrointestinal losses, and a shift of potassium from the extracellular into the intracellular compartment [1,2,4]. Symptomatic hypokalaemia usually occurs only in severe hypokalaemia and may present with cardiac arrhythmias and paralysis [1,2,4]. Hypokalaemia can be treated with oral or intravenous potassium suppletion and/or a potassium-sparing diuretic [2]. A potential risk of the management of hypokalaemia is the development of subsequent hyperkalaemia [5–7], which can also lead to potentially serious cardiac arrhythmias [8]. Potassium suppletion alone is unlikely to cause hyperkalaemia [8], but it is unclear which contributory factors are required. Therefore, in this observational study, the objective was to study the epidemiology of hypokalaemia in a general hospital population, specifically focusing on how often and why patients developed hyperkalaemia following hypokalaemia. For this purpose, we assessed factors contributing to hypokalaemia and subsequent hyperkalaemia in 140 patients with hypokalaemia.

Correspondence to: Ewout J. Hoorn, MD, Erasmus Medical Center, Dialysis Unit, Room Bd 391, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. Email: ejhoorn@gmail.com
The authors wish it to be known that, in their opinion, the first two authors contributed equally to this work.

Subjects and methods

Patients and laboratory measurements

In a study-period of 3 months (March–May 2004), we reviewed all ordered S_K-values and included all patients with hypokalaemia (S_K <3.5 mmol/l). Subsequently, we analysed which of these patients developed hyperkalaemia (S_K ≥5.0 mmol/l). Patients were admitted to the departments of internal medicine (including nephrology, endocrinology, haematology, infectious diseases, geriatrics, oncology, gastroenterology and pulmonology), surgery (including abdominal, vascular and plastic surgery, traumatology, transplantation, neurosurgery, orthopaedics, urology and ear-nose-and-throat), neurology and gynaecology in the Erasmus Medical Center, an 813-bed urban university hospital in Rotterdam, The Netherlands. S_K-values were determined with ion-selective electrodes (Hitachi 917, Roche, according to the manufacturer's instructions). Haemolytic samples were automatically reported by the clinical chemistry department and excluded from analysis. Patients with hyperkalaemia were screened for the likelihood of pseudohyperkalaemia by analysing leucocyte and thrombocyte counts [9,10]. Routine testing for familial pseudohyperkalaemia and heredity stomatocytosis was not available [11].

Data collection

Factors that may have contributed to hypokalaemia and/or subsequent hyperkalaemia were recorded. These included demographic data, biochemical parameters, underlying disorders, medication and in-hospital procedures. With regard to biochemistry, we focused on the serum sodium, creatinine and available magnesium and acid–base parameters. Hyponatraemia was defined as a serum sodium of <136 mmol/l, hypomagnesaemia as a serum magnesium of <0.70 mmol/l, hypophosphataemia as a serum phosphate of <0.90 mmol/l, and elevated creatinine as >90 μmol/l for females and as >115 μmol/l for males. Reference values for bicarbonate were 21–27 mmol/l, and for pCO_2 4.7–6.4 kPa. The total amount of potassium suppletion administered, either orally or intravenously, was calculated in millimolar (mmol) terms. The amount of potassium in total parenteral nutrition (Clinomel N6-900®, 48 mmol potassium per 2015 ml) was included in this calculation, whereas dietary potassium was not. Although we did look for less common hypokalaemic disorders, including Conn, Bartter and Gitelman syndromes, we did not routinely measure aldosterone levels or pursue genotyping. The diagnostic criteria for Conn's disease were hypertension, a positive aldosterone suppression test and the radiographic identification of an adrenal mass. We assessed subjective symptoms in patients with severe hypokalaemia (thirst, paraesthesias, muscle weakness and muscle cramps), but did not systematically perform electrocardiography in these patients. Data were collected by way of clinical examination of patients, the electronic hospital information system, chart-review and review of discharge letters. During the study-period, the treating physicians remained responsible for the care of the patients reported in this study.

Table 1. Demographics and course in serum potassium concentration in 140 patients with hypokalaemia

Demographics	
Age (years)	57 ± 17
Female sex, *n* (%)	73 (52)
Course serum potassium in groups	
Hypokalaemia on admission, *n* (%)	40 (29)
Hospital-acquired hypokalaemia, *n* (%)	100 (71)
Hospital-acquired hyperkalaemia, *n* (%)	23 (16)
Course serum potassium in numbers	
S_K admission (mmol/l)	3.9 ± 0.8
S_K lowest (mmol/l)	3.0 ± 0.3
S_K discharge/death (mmol/l)	4.0 ± 0.6
Period <3.5 mmol/l (days)	3.2 ± 2.4

S_K, serum potassium concentration.

Statistical analysis

To identify factors contributing to hyperkalaemia following hypokalaemia, we compared patients who developed hyperkalaemia to those who remained normokalaemic (S_K between 3.5 and 5.0 mmol/l) after hypokalaemia. First, univariate analyses were performed using Fisher's Exact test for categorical data and the non-parametric Mann–Whitney U rank sum test for continuous data. Subsequently, multivariate logistic regression was performed selecting the development of hyperkalaemia as a dependent and using a backward conditional approach. Data were analysed by SPSS (version 13.0, Chicago, IL). Data are expressed as mean ± SD, unless specified otherwise. Statistical significance was defined as $P \leq 0.05$.

Results

Epidemiology of hypokalaemia

From 1178 patients in whom S_K was measured, 140 patients (12%) with hypokalaemia were included in this 3-month hospital-wide study. Table 1 shows the demographic data and the course in serum potassium concentration during hospitalization. Patients were admitted to the departments of internal medicine (69 patients, 49%), surgery (56 patients, 40%), gynaecology (10 patients, 7%) and neurology (5 patients, 4%). Of these departments, the following subspecialties saw the most patients with hypokalaemia: nephrology (14 patients, 10%), haematology, gastro-enterology and neurosurgery (all three 13 patients or 9%). Forty patients (29%) had hypokalaemia on admission, while 100 patients (71%) developed hypokalaemia during hospitalisation. Fifty-six patients (40%) had at least one episode of severe hypokalaemia (S_K <3.0 mmol/l). Subjective symptoms in these 56 patients with severe hypokalaemia included thirst (24 patients, 43%), paraesthesias (21 patients, 38%), muscle weakness (8 patients, 14%) and muscle cramps (4 patients, 7%). After resolution of hypokalaemia, 23 patients (16%) developed hyperkalaemia (highest S_K 5.7 ± 0.7 mmol/l). Thirty-five patients (25%) were discharged with hypokalaemia (S_K 3.3 ± 0.2 mmol/l),

Table 2. Analysis of how often one or two factors were present during hypokalaemia

Factors (total number of patients)[a]	1	2	3	4	5	6	7	8	9
1 Vomiting ($n=56$)	13	14	20	13	13	9	8	1	0
2 Use of diuretics ($n=50$)		12	8	13	7	3	5	0	0
3 Diarrhoea ($n=40$)			6	17	7	5	4	0	1
4 Hypomagnesaemia ($n=40$)[b]				4	11	7	4	1	0
5 Hyperglycaemia ($n=27$)					1	11	3	2	0
6 Use of insulin ($n=16$)						0	2	1	1
7 Haematological malignancy ($n=13$)							0	1	0
8 Use of amphotericin B ($n=2$)								0	0
9 Conn's disease ($n=1$)									0

[a]Numbers 1–8 in the first column correspond to those in the first row; first diagonal row represents single causes, others a combination of two causes.
[b]When measured.

Table 3. Biochemical disorders associated with hypokalaemia

Biochemical disorders[a]	Measured in *n* (%)	Present in *n* (%) of measured	Serum values
Hyponatraemia	140 (100)	34 (24)	132 ± 3 mmol/l
Hypomagnesaemia	66 (47)	40 (61)	0.58 ± 0.09 mmol/l
Hypophosphataemia	62 (44)	21 (34)	0.67 ± 0.19 mmol/l
Elevated creatinine	137 (98)	24 (18)	129 (94–517) μmol/l[b]
Acid-base disorder	45 (32)	16 (36)	
– Metabolic alkalosis		5 (11)	HCO_3^- 30 ± 2 mmol/l
– Metabolic acidosis		3 (7)	HCO_3^- 19 ± 1 mmol/l
– Respiratory alkalosis		6 (13)	pCO_2 4.1 ± 0.8 kPa
– Respiratory acidosis		2 (4)	pCO_2 8.1 ± 2.2 kPa

[a]See methods for definitions.
[b]Mean and range are reported. Five patients on dialysis were excluded.
HCO_3^-, bicarbonate (reference 21–27 mmol/l); pCO_2, carbon dioxide pressure (reference 4.7–6.4 kPa).

while six patients (4%) were discharged with hyperkalaemia (S_K 5.4 ± 0.4 mmol/l). Nine patients (6%) died during the study period, including one patient with hypokalaemia (S_K 3.4 mmol/l), one patient with hyperkalaemia (S_K 5.9 mmol/l) and seven patients with normal S_K values (S_K 3.9 ± 0.4 mmol/l).

Causes of hypokalaemia and biochemical disorders associated with hypokalaemia

The most common factors contributing to hypokalaemia are shown in Table 2. The table shows how often one or a combination of two factors were present. For example, 14 patients had a combination of vomiting (row 1) and diuretic use (column 2, which corresponds with row 2). In 104 patients (74%) hypokalaemia appeared multifactorial (Table 2, calculated as the total number of 140 minus the sum of the numbers in first diagonal row, i.e. patients who had only one contributing factor of hypokalaemia). Table 3 shows which biochemical disorders were associated with hypokalaemia, based on an analysis of the available parameters. As shown, hyponatraemia (34 patients, 24%) and, when measured, hypomagnesaemia (40 patients, 61%) and hypophosphataemia (21 patients, 34%) were frequently present in patients with hypokalaemia. Of the 34 patients with hypokalaemia and hyponatraemia, 26 patients had gastrointestinal losses and 10 patients used diuretics. These two underlying factors were also common in hypokalaemia with hypomagnesaemia (Table 2).

Hyperkalaemia following hypokalaemia

As shown in Table 1, 23 patients (16%) developed hyperkalaemia following hypokalaemia.

Pseudohyperkalaemia as a cause for hyperkalaemia in the 23 patients appeared unlikely, since none of the samples were haemolytic and the average leucocyte and thrombocyte counts were not elevated ($7.2 \pm 5.2 \times 10^9$/l and $211 \pm 175 \times 10^9$/l, respectively). The individual S_K courses of these patients, from the lowest S_K (2.9 ± 0.4 mmol/l) until the highest S_K (5.7 ± 0.7 mmol/l) are shown in Figure 1A. To evaluate if the rise in S_K could be due to a concomitant deterioration of renal function, serum creatinine values of these patients were also plotted for the same time-period (Figure 1B). Although several patients had a degree of renal insufficiency, renal function deteriorated in few patients. To further analyse which factors contributed to the development of hyperkalaemia, we compared patients with hyperkalaemia to patients who remained normokalaemic after resolution of hypokalaemia (Table 4). Possible contributory factors were divided into four categories, including (i) factors associated with the treatment of hypokalaemia, (ii) factors associated with hypokalaemia due to a shift of potassium into cells, (iii) reduced renal potassium excretion and (iv) other factors known to be associated with hyperkalaemia [1,12]. Hypokalaemic patients who developed hyperkalaemia did not receive potassium more often (70% *vs* 59%, $P = 0.5$), but when potassium was given, the total dose was significantly higher (median 350 *vs* 180 mmol, $P = 0.02$). Potassium was always replaced as the chloride salt either orally or intravenously. Intravenous replacement of potassium was not more common in patients who became hyperkalaemic. Three additional factors were significantly more often present in patients who developed hyperkalaemia following hypokalaemia, namely magnesium suppletion (7/23 *vs* 10/117, $P = 0.009$), total parenteral nutrition (4/23 *vs* 4/117, $P = 0.02$) and haematological malignancy (5/23 *vs* 7/117, $P = 0.03$). Of the patients with hyperkalaemia, potassium suppletion was given to six of seven patients receiving magnesium suppletion and to all patients with haematological malignancy. Serum magnesium was measured in 15 of the 17 patients with magnesium suppletion. Eleven of these patients had hypomagnesaemia, including four of the seven patients with hyperkalaemia.

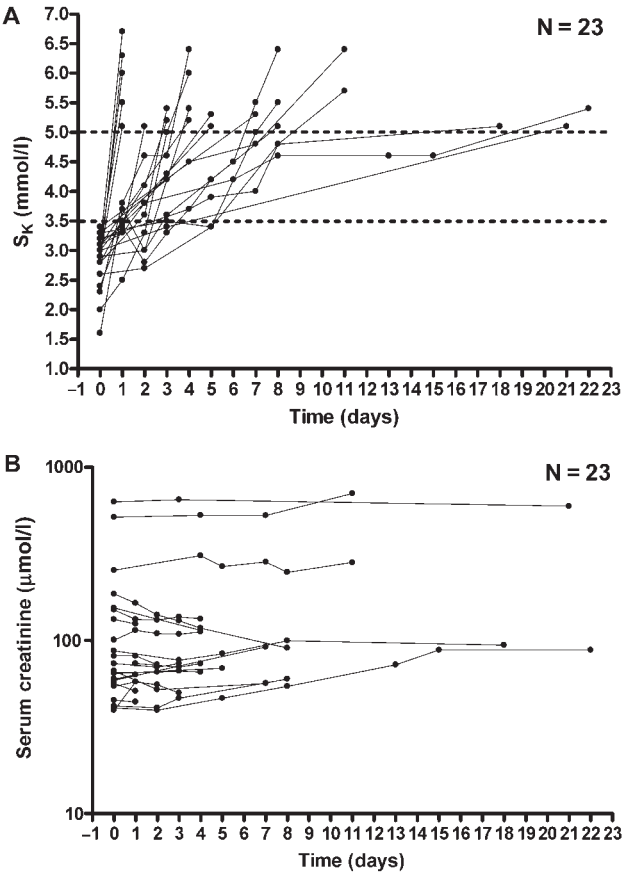

Fig. 1. Course plotted from lowest serum potassium (S_K) until highest S_K including all values measured in between. Dashed lines depict reference values for serum potassium. Log scale for serum creatinine. Serum potassium (**A**) and corresponding serum creatinine (**B**) courses in 23 patients with hyperkalaemia following hypokalaemia.

Independent risk factors for hyperkalaemia following hypokalaemia

In the next step of our analysis, we investigated which of the factors identified in the univariate analysis were independently associated with hyperkalaemia following hypokalaemia. For this purpose, we performed a multivariate logistic regression and included in the model the total potassium suppletion and the three significant variables from the univariate analysis (magnesium suppletion, total parenteral nutrition and haematological malignancy). This analysis showed that magnesium suppletion [odds ratio (OR) 6.6, 95% confidence interval (CI) 1.4–30.0], total parenteral nutrition (OR 10.0, 95% CI 1.4–73.7), and haematological malignancy (OR 24.3, 95% CI 3.5–170.1) were independent risk factors for hyperkalaemia following hypokalaemia, whereas total potassium suppletion was not.

Discussion

In this observational study we investigated the epidemiology of hypokalaemia in a general hospital population, and also focused on how often and why these patients developed subsequent hyperkalaemia. Hypokalaemia was frequently acquired in the hospital, was often multifactorial and frequently coexisted with hyponatraemia and hypomagnesaemia. One out of every six patients with hypokalaemia subsequently developed hyperkalaemia.

The question to answer is why patients developed hyperkalaemia following hypokalaemia. One obvious factor is the amount of potassium suppleted, which was indeed significantly higher in patients who developed hyperkalaemia (Table 4). However, as stated by Weiner and Wingo [8], potassium suppletion alone rarely produces hyperkalaemia in the absence of contributing factors. This is also illustrated by potassium loading studies in healthy volunteers whose kidneys are able to efficiently increase urinary potassium excretion [13]. Thus, the next question is which contributory factors were involved in the development of hyperkalaemia. Because we did not measure aldosterone levels and urinary electrolytes, we emphasise that it is difficult to identify the exact mechanisms that led to hyperkalaemia. Despite this restriction, we analysed two possible scenarios, including a reduction in renal potassium excretion, and a shift hypokalaemia, which often results in rebound hyperkalaemia [14]. Drugs inhibiting the renin angiotensin system or the aldosterone receptor are associated with hyperkalaemia [15–18], but they were not more commonly prescribed to our patients with hyperkalaemia. Similarly, although renal dysfunction was present in one-third of the patients with hyperkalaemia, the same was true for patients who remained normokalaemic. Finally, neither factors that stimulate a shift of potassium into cells (insulin, alkalosis) nor factors that prohibit this shift (beta-adrenergic factors) were more common in patients with hyperkalaemia. Importantly, the lack of statistical differences does not exclude the possibility that the *combination* between potassium suppletion and one of these factors caused an 'overshoot' hyperkalaemia. For example, the return of potassium to the extracellular fluid after a shift of hypokalaemia in combination with potassium suppletion may explain the development of hyperkalaemia within one day in some patients (Figure 1A),

Interestingly, three novel and independent factors associated with hyperkalaemia following hypokalaemia were identified, including total parenteral nutrition, magnesium suppletion and haematological malignancy. The possible role of these factors in hyperkalaemia will be discussed here. First, there is no literature to suggest an association between parenteral nutrition and hyperkalaemia. Therefore, we assume it was a surrogate marker for potassium suppletion. Indeed, the significant difference in total potassium suppletion between hyperkalaemic and normokalaemic patients disappeared when the amount of potassium in parenteral nutrition was left out. This emphasises that parenteral nutrition is a less visible, but important, source of potassium (approximately 20 mmol/l). Second, since

Table 4. Analysis of factors potentially contributing to hyperkalaemia following hypokalaemia

	Hyperkalaemia ($n = 23$)	No hyperkalaemia ($n = 117$)	P-value[a]
Factors associated with treatment of hypokalaemia			
Potassium suppletion, *n* (%)	16 (70)	69 (59)	0.5
Total potassium suppletion, mmol, median (range)[b]	350 (118–2288)	180 (20–1512)	0.02
Intravenous administration, *n* (%)	13 (56)	37 (32)	0.3
Magnesium suppletion, *n* (%)	7 (30)	10 (9)	0.009
Total parenteral nutrition, *n* (%)	4 (17)	4 (3)	0.02
Factors associated with hypokalaemia due to a shift			
Use of insulin (at time of hypokalaemia), *n* (%)	4 (17)	12 (10)	0.3
Alkalosis (at time of hypokalaemia), *n* (%)	0 (0)	11 (9)	0.3
β-adrenergic blockers, *n* (%)	7 (30)	25 (21)	0.4
Reduced renal potassium excretion			
Renal dysfunction, *n* (%)	7 (30)	35 (30)	1.0
Potassium sparing diuretics, *n* (%)	1 (4)	15 (13)	0.5
Angiotensin converting enzyme inhibitors, (%)	3 (13)	9 (8)	0.4
Other factors associated with hyperkalaemia			
Haematological malignancy, *n* (%)	5 (22)	7 (6)	0.03

[a]Comparing patients who developed hyperkalaemia following hypokalaemia *vs* patients who remained normokalaemic after hypokalaemia.
[b]Calculated as the sum of the daily doses from start until finish of potassium suppletion.

hypomagnesaemia is associated with a kaliuresis [19–22], correction of hypomagnesaemia with magnesium suppletion may reduce kaliuresis and thus renal potassium excretion. Luminal calcium can inhibit the activity of the epithelial sodium channel and thereby active potassium secretion [23], but it is not known if magnesium can have similar effects. In theory, any compound that interferes with the transepithelial potential difference could reduce potassium secretion and thereby contribute to hyperkalaemia [1]. Third, increased release of potassium into the extracellular fluid volume could be a feasible mechanism in haematological malignancy if for example cancer treatment resulted in the tumour lysis syndrome, in which hyperkalaemia is a common complication [12,24,25]. It appears paradoxical that haematological malignancy was associated with both hypokalaemia and hyperkalaemia. A possible explanation is that hypokalaemia on admission was due to the underlying disease [26–28], whereas subsequent hyperkalaemia was caused by tumour lysis in combination with potassium suppletion [12,24,25].

The clinical recommendations that follow from our study are to exert caution with potassium suppletion, especially in patients who also receive magnesium suppletion or total parenteral nutrition, or in patients treated for haematological malignancy. This should include frequent monitoring of S_K and withdrawal of potassium suppletion when hyperkalaemia ensues. Another way to help prevent derangement of electrolyte balance and to improve the overall management of hypokalaemia, could be to implement a hospital warning system using a computerised alert [29,30]. Recently, hyperkalaemia has mainly received attention as a side-effect of drugs acting on the renin angiotensin system or the aldosterone receptor [15–18]. Thus, paradoxically, this study adds the management hypokalaemia to the list of risk factors for hyperkalaemia.

Beside hyperkalaemia following hypokalaemia, another interesting epidemiological finding was the high incidence of hospital-acquired hypokalaemia. Almost three out of every four patients developed hypokalaemia in the hospital, a percentage that is higher than reported previously [3,31]. This percentage is also higher than for other electrolyte disorders, for example hospital-acquired hyponatraemia [32]. To prevent hospital-acquired hypokalaemia and the associated dangers, a fall in S_K in the hospital should lead to the identification of the underlying causes and the start of monitored potassium suppletion, if necessary.

With regard to the pathogenesis of hypokalaemia, we identified gastrointestinal losses, diuretics and hypomagnesaemia as the most common factors contributing to hypokalaemia. This is similar to what previous studies found [3,31,33]. Our analysis also shows that a combination of factors was often present, for example vomiting and diarrhoea or diarrhoea and hypomagnesaemia, indicating a multifactorial origin of hypokalaemia. This suggests that at least two factors may be necessary to overwhelm homeostatic control mechanisms and result in overt hypokalaemia.

Hypokalaemia frequently coexisted with hyponatraemia, which has only been described anecdotally [34,35]. Gastrointestinal losses and the use of diuretics appeared to be associated with this concurrence [35]. In patients with hypokalaemia and hyponatraemia due to renal losses, one could consider treating both conditions simultaneously, for example with isotonic intravenous fluids with added potassium [36]. In addition, we found that, when serum magnesium was determined, the incidence of hypomagnesaemia was substantial, confirming previous observations [37]. Because of the close association between hypokalaemia and hypomagnesaemia, a case can be made for a standard determination of serum magnesium with potassium [37–39]. Whang and Ryder [40] illustrated

this point even more poignantly, by showing that less than 10% of physicians ordered magnesium in over 1000 specimens submitted for electrolyte analysis, while magnesium abnormalities were found in approximately 50%. Although gastrointestinal losses and diuretics were the main causes for combined potassium and magnesium deficiency [41], there is also evidence that hypomagnesaemia can directly cause hypokalaemia by stimulating a kaliuresis [19–22]. The molecular background between these interactions remains incompletely understood, although there may be a role for the transient receptor potential channel subfamily M, member 6 (Trpm6). For example, Trpm6 was downregulated with thiazide use and in Gitelman's syndrome, in which there is often, but not always, a combination of hypokalaemia and hypomagnesaemia [42]. Finally, hypophosphataemia was seen in a third of the patients in whom it was measured, and the most likely explanations for combined hypokalaemia and hypophosphataemia include redistribution (e.g. during acute respiratory alkalosis), intestinal losses or urinary losses (e.g. during an osmotic diuresis or with Fanconi syndrome) [39].

This is one of the largest cohorts of hypokalaemic patients described in the literature. However, the limitations of this study are its observational character and the lack of urinary data and aldosterone levels, which would be required to identify specific mechanisms of hypokalaemia and subsequent hyperkalaemia.

In conclusion, hypokalaemia is a multifactorial and usually hospital-acquired condition associated with hyponatraemia and hypomagnesaemia. One out of every six patients with hypokalaemia developed subsequent hyperkalaemia. Besides potassium suppletion, total parenteral nutrition (source of potassium), magnesium suppletion (may reduce kaliuresis) and haematological malignancy (may cause cell lysis) contribute to hyperkalaemia following hypokalaemia. Caution with potassium suppletion and frequent monitoring of S_K may prevent iatrogenic hyperkalaemia.

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