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Hyperkalemia in Two Patients with Diabetes Mellitus and Chronic Kidney Disease and the Role of Disrupted Internal Potassium Balance

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Abstract

To identify factors associated with the development of hyperkalemia in patients with chronic kidney disease (CKD), we analyzed conditions present during episodes of hyperkalemia in two patients with insulin-dependent diabetes mellitus who had elevated serum potassium concentration ([K]) in ⩾ 20% of the blood samples during both the pre-hemodialysis and the hemodialysis period. In both patients, conditions causing derangements in the internal potassium balance (exchanges of potassium between the intracellular and the extracellular compartment), including severe hyperglycemia (serum glucose concentration ⩾ 400 mg/dL) and catabolic illnesses, were present in ⩾ 75% of the instances of simple hyperkalemia ([K] ⩾ 5.1 mmol/L) and almost all of the instances of severe hyperkalemia ([K] ⩾ 6.0 mmol/L) during both the pre-hemodialysis and the hemodialysis periods. Derangements of the internal potassium balance, many of which are potentially preventable, can be a major cause of hyperkalemia in patients with CKD before or after starting chronic hemodialysis. Careful analysis of the conditions associated with and potentially causing hyperkalemia in CKD patients is imperative for both treatment and prevention purposes.

Categories: Endocrinology/Diabetes/Metabolism, Internal Medicine
Keywords: hyperkalemia, hyperglycemia, catabolic illness, chronic kidney disease, hemodialysis, diabetes mellitus

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Introduction

Hyperkalemia, even at modest levels, is associated with adverse outcomes, including shortened survival, in the general population [1]. Evaluation of the pathogenetic mechanism(s) of each episode of hyperkalemia is required for both treatment and prevention. The concentration of potassium in serum ([K]) is determined by the interplay of two balances, the external balance (intake and output of potassium) and the internal balance (potassium exchanges between the intracellular and extracellular compartments). Either or both mechanisms may be at fault in each episode of hyperkalemia [2].

The frequency of hyperkalemia is high in patients with chronic kidney disease (CKD) [3] and even higher in those on chronic hemodialysis [4]. Defects in both the external and internal

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potassium balance have been documented in CKD. Patients with CKD have limited capacity to excrete potassium loads [5]. Advanced CKD leads also to defective uptake of potassium by cells as a consequence of uremia [6]. We present two patients with insulin-dependent diabetes mellitus and CKD who had a high frequency of hyperkalemia (in ⩾ 20% of the serum samples) in both the pre-hemodialysis (pre-HD) and the hemodialysis (HD) periods. The purpose of this report was to investigate mechanisms of hyperkalemia in these patients and to compare the pre-HD and HD periods.

Case Presentation

Patients

Both patients were men with insulin-dependent diabetes mellitus. Table *1* shows age at initiation of dialysis, duration of follow-up pre-HD and during the HD period, and annual hospitalization rates, plus average days of hospitalization per annum. The table also shows the 95% confidence interval (CI) of the corresponding values for a control group comprised of all other diabetic men treated in the same dialysis unit over the same period [7]. The control group was used only for comparison of morbidity with the two patients presented. Hospitalization was used as the measure of morbidity. The ages of the two patients at initiation of hemodialysis and the duration of follow-up in the pre-HD and HD periods were within the corresponding 95% CIs of the control group. The rates and lengths of hospitalizations exceeded the corresponding upper limits of the 95% CIs intervals of the control group in both the pre-HD and HD periods in both patients.

	Patient 1	Patient 2	Controls*
Age at HD initiation, years	56.1	51.1	65.2 (45.4-85.0)
Pre-HD follow-up period, years	3.83	8.42	5.42 (0-10.84)
HD follow-up period, years	1.90	3.75	2.55 (0-5.10)
Hospitalization rate, pre-HD period, n/yr	5.48	0.83	0.62 (0.53-0.71)
Hospitalization rate, HD period, n/yr	6.32	5.33	2.42 (2.16-2.68)
Hospital days per year, pre-HD period	38.1	9.6	5.2 (4.1-6.3)
Hospital days per year, HD period	45.8	38.7	32.5 (26.2-33.8)

TABLE 1: Ages and hospitalizations

HD = hemodialysis. * 232 hemodialysis patients with diabetes mellitus [7]. The numbers in the Controls column show mean (95% Confidence Interval)

The course of both patients during the pre-HD and HD periods was characterized by repeated episodes of severe hyperglycemia and episodes of catabolic illness. In the first patient, catabolic illnesses included left leg gangrene leading to high below-the-knee amputation with prolonged postoperative sepsis, sepsis secondary to an infected dialysis catheter, and sepsis associated with severe pneumonia. The second patient had repeated episodes of deep abscesses secondary to self-injection of illegal drugs, large muscle hematoma secondary to trauma, infectious endocarditis, and right femoral neck fracture with operative correction. Patient 1 died suddenly at home. Patient 2 expired two months after the repair of

the right hip fracture after withdrawing all treatments.

Methods

The following additional information was collected for each patient in both the pre-HD and HD periods: (a) Medications that affect internal or external potassium balance, including insulin, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β_2-adrenergic blocking agents, potassium salts, diuretics, sodium polystyrene sulfonate, and β_2-adrenergic agonists; (b) presence or absence of catabolic illness at the time of each blood sampling; (c) serum chemistries, including glucose, sodium, potassium, chloride, total carbon dioxide ([TCO_2]), urea nitrogen (SUN) and creatinine concentrations, and arterial blood gases; (d) whether the laboratory tests were collected in an outpatient setting or during hospitalization, whether episodes of hyperglycemia were associated with ketoacidosis, and whether laboratory tests obtained after a test showing severe hyperglycemia were collected during treatment of this hyperglycemic episode with continuous insulin infusion. [K] ⩾ 5.1 mmol/L was considered hyperkalemia, while [K] ⩾ 6.0 mmol/L was considered severe hyperkalemia [3]. Finally, the following derived parameters were calculated:

Serum tonicity (effective osmolarity) = 2x[Na] + [Glu]/18, where tonicity is in mOsm/L, glucose concentration ([Glu])is in mg/dL, and [Na] is serum sodium concentration [8].

Serum osmolarity = Tonicity + [Urea], where [Urea] is serum urea concentration calculated as SUN/2.8 [8].

[Na] was corrected to a serum glucose level of 100 mg/dL [9-10]. Corrected serum sodium values ($[Na]_{Corr}$) were calculated for all serum samples as follows: $[Na]_{Corr}$ = [Na] + 1.6x([Glu] – 100)/100

Serum anion gap in mEq/L = [Na] – ([Cl] + [TCO_2]), where [Cl] is the serum chloride concentration.

Statistical methods

Continuous variables are presented as mean ± standard deviation. Initial statistical analysis addressed the pre-HD and HD periods combined. The relationship between parametric variables and [K] was evaluated by correlational analysis. For categorical variables, [K] values obtained while the variable was present were compared by unpaired student's t-test to [K] values obtained when the variable was absent. Hyperglycemia and the presence of catabolic illness were the two most prominent conditions associated with hyperkalemia in both patients. [Glu] levels ⩾ 400 mg/dL are reported as critical by the laboratory of this hospital and were considered "severe" hyperglycemia for this report. Serum samples with [Glu] < 400 mg/dL obtained in periods when catabolic illness was absent were labeled as control samples. In the pre-HD and HD periods separately, [K] levels were compared between hyperglycemic and control samples in two ways: In the first comparison, the control sample (Control 1) was the closest control sample preceding or following the hyperglycemic sample. The comparison was performed by paired t-tests. In the second comparison, all control samples (Control 2) were compared to the hyperglycemic samples by unpaired student's t-tests. For these comparisons, serum samples obtained during treatment of a hyperglycemic episode with continuous insulin infusion were excluded from both the hyperglycemic and control categories. [K] values in serum samples without hyperglycemia obtained during catabolic illness activity were compared to [K] values in control samples (Control 2 above) by unpaired student's t-tests.

Linear regression of [K] on [Glu] was performed separately in the pre-HD and HD periods. The samples analyzed in the regressions included all control samples and hyperglycemic samples, with three exceptions: Serum samples obtained during episodes of ketoacidosis, during treatment of hyperglycemia with continuous insulin infusion, and during episodes of catabolic illness were excluded from this statistical analysis.

Stepwise, multiple linear regression was performed in each patient to identify predictors of [K]. A forward and backward stepping procedure was used with a P-value < 0.05 to enter and > 0.05 to remove a variable. The candidate variables included the period of observation (pre-HD vs. HD), the presence or absence of ketoacidosis, whether the blood sample was obtained during hospitalization or on an outpatient basis, whether the blood test was obtained during continuous infusion of insulin during treatment of severe hyperglycemia, presence or absence of catabolic illness, intake of drugs affecting potassium balance, and parametric variables, such as [Glu], SUN, tonicity, and $[Na]_{Corr}$. All serum samples were included in this analysis.

Results

The first patient had, during the pre-HD period, 223 measurements of serum chemistries. Seventy-nine of these measurements (35.3%) exhibited hyperkalemia ([K] range 5.1-9.1 mmol/L) and 19 measurements (8.5%) exhibited severe hyperkalemia. Among 170 measurements during the HD period in the same patient, 50 (29.4%) exhibited hyperkalemia ([K] range 5.1-8.8 mmol/L) and 14 (8.2%) exhibited severe hyperkalemia. The second patient had 100 measurements in the pre-HD period. Twenty of these measurements (20.0%) exhibited hyperkalemia ([K] range 5.1-7.2 mmol/L) and three measurements (3.0%) exhibited severe hyperkalemia. Among 213 measurements in the same patient during the HD period, 63 (29.6%) exhibited hyperkalemia ([K] range 5.1-7.5 mmol/L) and 19 (8.9%) exhibited severe hyperkalemia.

When all serum samples obtained in the pre-HD and HD periods were analyzed together, [K] values correlated with the following parameters in the first patient: [Glu] (r = 0.846), [Na] (r = -0.722), tonicity (r = 0.810), osmolarity (r = 0.801), [Cl] (r = -0.709), $[TCO_2]$ (r = -0.653), and serum anion gap (r = 0.653). In the second patient, correlated with [Glu] (r = 0.569), [Na] (r = -0.642), tonicity (r = 0.323), osmolarity (r = 0.414), [Cl] (r = -0.631), $[TCO_2]$ (r = -0.715), and serum anion gap (r = 0.668) [P < 0.001 for all]. In both patients, all other parameters correlating with [K] correlated strongly with [Glu]. Their correlations had, in every instance, the same sign as the correlation between [K] and [Glu] suggesting that changes in [Glu] were probably the main cause of these correlations.

Tables *2*-*7* show comparisons of laboratory tests between episodes of hyperglycemia and control states (Tables *2*-*5*) and between episodes of catabolic illness and control states (Tables *6*, *7*). The control states of absence of severe hyperglycemia and catabolic illness in the same patients (not in the control group of patients used for comparison of morbidity in Table *1*) were defined in the Methods subsection. The bodies of Tables *2*-*7* show the comparison of the mean values, while the captions of the Tables show the number (percent) of the [K] measurements that were in the hyperkalemic range in each column. Tables *2*, *3* compare biochemical values between the episodes of non-ketotic hyperglycemia and the two control states in Patients 1 and 2, respectively. Tables *4*, *5* show the same values for episodes of diabetic ketoacidosis. Average [K] values were significantly higher at hyperglycemia than in either control stage in the pre-HD and HD periods in both patients. Substantially higher percentages of [K] levels were in the hyperkalemic range at hyperglycemia than in the control states. The highest [K] values were observed in episodes of diabetic ketoacidosis.

	Pre-HD Period	→	→	HD Period	→	→
	Hyperglycemia	Control 1	Control 2	Hyperglycemia	Control 1	Control 2
Sample Number	36	36	109	31	31	43
Glucose, mg/dL	628±172	148±86**	178±103**	595±202	135±93**	182±90**
Potassium, mmol/L	5.28±0.86[1]	4.34±0.67**[2]	4.34±0.72*[3]	5.39±1.04[4]	4.36±0.61*[5]	4.21±0.52**[6]
Sodium, mmol/L	129.2±3.9	137.1±4.1**	137.7±3.2**	129.4±4.6	135.6±3.2**	135.0±4.6**
Corrected sodium, mmol/L	137.4±3.0	137.9±2.7	139.0±2.7	137.2±2.7	136.2±3.0	136.3±4.6
Tonicity, mOsm/L	292.3±9	282.3±7**	280±6**	292±7	279±6**	280±10**
SUN, mg/dL	45±13	45±13	45±18	37±15	38±15	38±12
Osmolarity mOsm/L	309±8	298±9**	301±8*	305±8	292±7**	294±10
Chloride, mmol/L	98.0±5.3	104.7±5.6**	105.3±4.8**	95.1±5.3	100.7±5.5*	101.1±6.0**
TCO_2, mmol/L	22.8±3.3	23.7±3.4	24.7±3.1	25.1±4.7	26.6±4.5	25.4±3.5
Anion gap, mEq/L	8.8±6.8	8.1±3.6	7.7±3.3	8.3±3.6	7.7±3.0	8.5±3.4
Creatinine, mg/dL	2.53±0.50	2.47±0.97	2.70±1.17	4.34±1.10	4.15±1.20	3.50±1.20

TABLE 2: Serum concentrations at nonketotic hyperglycemia and control states. Patient 1

* p < 0.05; ** p < 0.01. HD = hemodialysis; SUN = serum urea nitrogen; TCO2 = total carbon dioxide. 1: > 5.0 mmol/L 22/36 (61.1%), > 5.9 mmol/L 9/36 (25.0%); 2: > 5.0 mmol/L 4/36 (11.1%), > 5.9 mmol/L 0/36 (zero) 3: > 5.0 mmol/L 18/109 (16.5%), > 5.9 mmol/L 3/109 (2.8%) 4: > 5.0 mmol/L 20/31 (54.5%), > 5.9 mmol/L 7/31 (ss.6%); 5: > 5.0 mmol/L 4/31 (12.9%), > 5.9 mmol/L 0/31 (zero) 6: > 5.0 mmol/L 2/43 (4.7%), > 5.9 mmol/L 0/43 (zero)

	Pre-HD Period	→	→	HD Period	→	→
	Hyperglycemia	Control 1	Control 2	Hyperglycemia	Control 1	Control 2
Sample Number	23	23	52	19	19	116
Glucose, mg/dL	587±123	156±68*	175±98**	497±68	112±63**	179±89**
Potassium, mmol/L	5.08±0.78[1]	4.21±0.48*[2]	4.37±0.54**[3]	5.07±1.12[4]	4.47±0.73*[5]	4.28±0.65**[6]
Sodium, mmol/L	130.4±3.1	134.4±3.7*	135.0±3.6**	133.4±4.0	135.9±4.4	136.6±2.9**
Corrected sodium, mmol/L	138.2±2.7	135.4±3.8	136.2±3.2	139.8±3.9	136.2±4.3	137.9±3.0
Tonicity, mOsm/L	293±6	277±8**	280±7**	294±9	280±106*	283±7**
SUN, mg/dL	38±21	36±19	38±18	48±14	45±16	39±18
Osmolarity, mOsm/L	307±9	290±9**	293±9**	312±8	295±9**	297±8**
Chloride, mmol/L	94.3±4.	100.2±3.1*	102.1±3.7**	95.9±4.5	99.2±4.5	99.2±4.0
TCO_2, mmol/L	23.7±3.4	24.2±3.3	23.3±3.6	18.0±2.8	21.8±2.8	22.7±3.9
Anion gap, mEq/L	12.4±4.1	10.0±2.9	9.5±3.5	18.5±4.9	14.6±4.7	14.6±4.6
Creatinine, mg/dL	2.68±1.75	2.68±1.99	3.20±1.85	5.28±1.83	5.51±1.94	5.45±1.96

TABLE 3: Serum concentrations at nonketotic hyperglycemia and control states. Patient 2.

* p < 0.05; ** P < 0.01. HD = hemodialysis; SUN = serum urea nitrogen; TCO2 = total carbon dioxide; 1: > 5.0 mmol/L 12/23 (52.2%), ≥ 6.0 mmol/L 3/23 (13.0%); 2: > 5.0 mmol/L 1/23 (4.3%), ≥ 6.0 mmol/L 0/23 (zero) 3: > 5.0 mmol/L 3/52 (5.8%), ≥ 6.0 mmol/L 0/52 (zero) 4: > 5.0 mmol/L 10/19 (52.6%), ≥ 6.0 mmol/L 5/19 (26.3%); 5: > 5.0 mmol/L 4/19 (21.1%), ≥ 6.0 mmol/L 0.19 (zero) 6: > 5.0 mmol/L 15/116 (12.9%), ≥ 6.0 mmol/L 0/116 (zero)

	Pre-HD Period	→	→	HD Period	→	→
	Ketoacidosis	Control 1	Control 2#	Ketoacidosis	Control 1	Control 2#
Sample number	3	3	109	5	5	43
Glucose, mg/dL	1350±260	199±54	178±103	1422±331	99±77	182±90
Potassium, mmol/L	7.60±1.67[1]	3.80±0.76[2]	4.34±0.72[3]	7.08±0.77[4]	3.92±0.64[5]	4.21±0.52[6]
Sodium, mmol/L	118.0±3.0	141.0±4.6	137.7±3.2	117.8±6.6	132.6±5.8	135.0±4.6
Corrected sodium, mmol/L	138.0±2.3	141.3±4.0	139.0±2.7	139.0±2.7	132.4±7.1	136.3±4.6
Tonicity, mOsm/L	311±10	289±7	285±6	315±8	271±15	280±10
SUN, mg/dL	83±28	82±21	45±18	38±11	59±25	38±12
Osmolarity, mOsm/L	341±15	318±2	301±8	332±9	292±10	294±10
Chloride, mmol/L	82.0±9.6	107.3±4.9	105.3±4.8	75.6±5.8	93.8±3.0	101.1±6.0
TCO_2, mmol/L	8.0±2.6	22.3±2.9	24.7±3.1	10.8±1.3	30.6±1.9	25.4±3.5
Anion gap, mEq/L	28.0±8.7	13.3±1.5	7.7±3.3	31.4±5.5	8.2±2.7	8.5±3.4
Creatinine, mg/dL	4.87±2.45	4.14±1.44	2.70±1.17	4.55±0.70	4.39±0.38	3.50±1.20
Arterial pH	7.13±0.08	-	-	7.20±0.01*	-	-
P_aCO_2, mm Hg	23.3±10.3	-	-	27.0±15.6*	-	-
Arterial HCO_3, mEq/L	9.7±2.0	-	-	11.9±3.4&	-	-

TABLE 4: Serum concentrations and arterial blood gases at diabetic ketoacidosis and control states. Patient 1

Same as Control 2 in Table 2; & arterial blood gases were available in only two of the five episodes of ketoacidosis. ketoacidosis HD = hemodialysis; SUN = blood urea nitrogen; TCO2 = total carbon dioxide; HCO3 = calculated bicarbonate from arterial blood gases; 1: ≥ 6.0 mmol/L 2/3 (66.7%); 2: > 5.0 mmol/L 0/3 (zero); 3: > 5.0 mmol/L 18/109 (16.5%), ≥ 6.0 mmol/L 3/109 (2.8%) 4: ≥ 6.0 mmol/L: 5/5 (100%); 5: > 5.0 mmol/L (0/5) (zero); 6: > 5.0 mmol/L 2/43 (4.7%) (%), ≥ 6.0 mmol/L 0/43 (zero)

	Ketoacidosis	Control 1	Control 2#
Sample number	3	3	116
Glucose, mg/dL	819±32	166±45	179±89
Potassium, mmol/L	6.87±0.76[1]	4.10±0.27[2]	4.28±0.65[3]
Sodium, mmol/L	133.7±1.5	138.7±0.6	136.6±2.9
Corrected sodium, mmol/L	145.2±2.0	139.8±0.8	137.9±3.0
Tonicity, mOsm/L	313±5	287±2	283±7
SUN, mg/dL	44±1	44±17	39±18
Osmolarity, mOsm/L	329±5	302±7	297±8
Chloride, mmol/L	90.3±1.5	100.7±0.6	99.2±4.0
TCO_2, mmol/L	5.3±2.3	23.3±2.1	22.7±3.9
Anion gap, mEq/L	38.0±0	14.7±1.5	14.6±4.6
Creatinine, mg/dL	6.43±0.25	5.90±0.99	5.45±1.96
Arterial pH	7.08±0.10	-	-
P_aCO_2, mm Hg	15.0±11.3	-	-
Arterial HCO_3, mEq/L	7.5±3.9	-	-

TABLE 5: Serum concentrations and arterial blood gases at diabetic ketoacidosis and control states. Patient 2, HD period

Same as Control 2 in Table 3. HD = hemodialysis; SUN = blood urea nitrogen; TCO2 = total carbon dioxide; HCO3 = calculated bicarbonate from arterial blood gases. 1 ≥ 6.0 mmol/L 3/3 (100); 2 > 5.0 mmol/L 0/3 (zero); 3 > 5.0 mmol/L 15/116 (12.9%), ≥ 6.0 mmol/L 0/116 (zero)

When all the samples in the pre-HD and HD periods were analyzed together for categorical variables, [K] values were statistically higher in Patient 1 during episodes of catabolic illness (179 samples) versus all other samples (4.86±0.95 vs. 4.59±0.92 mmol/L, p = 0.005). In the second patient, [K] levels were higher than in other samples during episodes of catabolic illness (106 samples, 4.89±1.01 vs. 4.41±0.76 mmol/L, p < 0.001) and during periods of beta-blocker treatment (42 samples, 5.00±1.11 vs. 4.53±0.81 mmol/L, p = 0.011), and lower than in other samples during periods of sodium polystyrene sulfonate treatment (35 samples, 4.17±0.75 vs. 4.65±0.87 mmol/L, p = 0.001) and intake of loop diuretics (n = 266 samples, 4.56±0.91 vs. 4.79±0.64 mmol/L, p = 0.036). [K] values were significantly higher during acting catabolic illness than during the control periods in the pre-HD period in Patient 1 (Table *6*) and during the HD period in Patient 2 (Table *7*) .

	Pre-HD Period	→	HD Period	→
	Catabolic Illness	Control#	Catabolic Illness	Control#
Sample Number	63	109	77	43
Potassium, mmol/L	5.00±0.53[1]	4.34±0.72**[2]	4.42±0.78[3]	4.21±0.52[4]
Glucose mg/dL	157±96	178±103	152±87	182±90
Sodium, mmol/L	135.8±3.1	137.7±3.2**	135.9±3.3	135.0±4.6
Corrected sodium, mmol/L	136.7±2.7	139.0±2.7**	136.8±9.1	136.3±4.6
Tonicity, mOsm/L	280±6	285±6**	280±6	280±10
SUN, mg/dL	49±10	45±18	35±18	38±12
Osmolarity, mOsm/L	298±7	301±8**	293±9	294±10
Chloride, mmol/L	105.9±4.5	105.3±4.8	101.5±5.8	101.1±6.0
TCO_2, mmol/L	22.4±2.2	24.7±3.1**	28.0±5.3	25.4±3.5**
Anion gap, mEq/L	7.5±2.3	7.7±3.3	6.5±2.7	8.5±3.4**
Creatinine, mg/dL	2.53±0.43	2.70±1.17	4.06±0.93	3.50±1.20**

TABLE 6: Serum concentrations at the stage of catabolic illness and at the control stage. Patient 1

* p , 0.05; ** p < 0.01. # Same as Control 2 in Table 2; HD = hemodialysis; SUN = serum urea nitrogen; TCO2 = total carbon dioxide; 1: >5.0 mmol/L 30/63 (47.6%), ≥ 6.0 mmol/L 1/63 (1.6%); 2: >5.0 mmol/L 18/109/ (16.5%), ≥ 6.0 mmol/L 3/109 (2.8%) 3: >5.0 mmol/L 20/77 (26.0%), ≥ 6.0 mmol/L 2/77 (2.6%) 4: >5.0 mmol/L 2/43 (4.7%), ≥ 6.0 mmol/L 0/43 (zero)

	Pre-HD Period	→	HD Period	→
	Catabolic Illness	Control#	Catabolic Illness	Control#
Sample Number	24	52	67	116
Potassium mmol/L	4.27±0.77[1]	4.37±0.54[2]	5.01±0.99[3]	4.28±0.65**[4]
Glucose mg/dL	170±89	175±98	174±94	179±89
Sodium mmol/L	136.2±2.5	135.0±3.6	135.4±3.2	136.6±2.9*
Corrected sodium mmol/L	137.3±2.6	136.2±3.2	136.6±3.4	137.9±3.0*
Tonicity mOsm/L	282±6	280±7	280±8	283±7*
SUN mg/dL	37±11	38±18	50±17	39±18**
Osmolarity mOsm/L	295±7	293±9	298±8	297±8
Chloride mmol/L	104.1±3.1	102.1±3.7*	100.4±3.8	99.2±4.0
TCO_2 mmol/L	21.5±2.8	23.3±3.6*	20.0±3.8	22.7±3.9**
Anion gap mEq/L	10.5±2.8	9.5±3.5	15.0±4.0	14.6±4.6
Creatinine mg/dL	3.39±1.35	3.20±1.85	5.67±1.90	5.45±1.96

TABLE 7: Serum concentrations at the stage of catabolic illness and at the control stage. Patient 2

* p < 0.05; ** p < 0.01. # Same as Control 2 in Table 3; HD = hemodialysis; SUN = serum urea nitrogen; TCO2 = total carbon dioxide. 1: >5.0 mmol/L 5/24 (20.8%), ≥ 6.0 mmol/L 0/24 (zero); 2: >5.0 mmol/L 3/52 (5.7%), ≥ 6.0 mmol/L 0/52 (zero) 3: >5.0 mmol/L 32/67 (47.8%), ≥ 6.0 mmol/L 10/67 (14.9%); 4: >5.0 mmol/L 15/116 (12.9%), ≥ 6.0 mmol/L 0/116 (zero)

Linear regressions of [K] on [Glu] were as follows:

Patient 1, pre-HD period: $[K] = 3.970 + 0.002x[Glu]$, $r^2 = 0.278$, $p < 0.001$

Patient 1, HD period: $[K] = 3.879 + 0.002x[Glu]$, $r^2 = 0.294$, $p < 0.001$

Patient 2, pre-HD period: $[K] = 4.039 + 0.002x[Glu]$, $r^2 = 0.080$, $p < 0.001$

Patient 2, HD period: $[K] = 4.079 + 0.002x[Glu]$, $r^2 = 0.337$, $p < 0.001$

The slope of the regressions was exactly the same (0.002 mmol/L rise in [K] per 1 mg/dL rise in [Glu]) for all four regressions. Standard regression diagnostics showed that the assumptions of linearity, homoscedasticity, and normality were justified for all four regressions.

Tables *8*, *9* show the predictors of [K] by multiple linear regression. In Patient 1, high values of [Glu] and SUN, catabolic illness, and use of ACE inhibitors or ARBs were independent predictors

of higher [K] values, while the pre-HD period, the period of continuous insulin infusion for treatment of severe hyperglycemia and periods of hospitalization were independent predictors of lower [K] values. For Patient 2, high values of [Glu] and SUN and catabolic illness were independent predictors of higher [K] values, while the pre-HD period, the period of continuous insulin infusion for treatment of severe hyperglycemia and use of sodium polystyrene sulfonate and diuretics were independent predictors of lower [K] values.

Variable	Regression Coefficient	Standard Error	P-Value	r^2
Serum glucose	0.002	< 0.001	< 0.001	
Serum urea nitrogen	0.008	0.002	< 0.001	
Hemodialysis period	-0.234	0.086	0.007	
During insulin infusion	-1.024	0.159	< 0.001	
During hospitalization	-0.408	0.118	0.001	
Catabolic illness	0.591	0.088	< 0.001	
Use of ACE inhibitor or ARB	0.382	0.125	0.002	
Constant	4.008	0.142	< 0.001	0.397

TABLE 8: Predictors of serum potassium concentration. Multiple linear regression in Patient 1

ACE = angiotensin converting enzyme. ARB = angiotensin receptor blocker.

Variable	Regression Coefficient	Standard Error	P-Value	r^2
Serum glucose	0.002	< 0.001	< 0.001	
Serum urea nitrogen	0.017	0.002	< 0.001	
During insulin infusion	-0.910	0.146	< 0.001	
Catabolic illness	0.744	0.091	< 0.001	
Use of sodium polystyrene sulfonate	-1.082	0.134	< 0.001	
Use of loop diuretics	-0.288	0.105	0.006	
Constant	3.620	0.129	< 0.001	0.456

TABLE 9: Predictors of serum potassium concentration. Multiple linear regression in Patient 2.

When several other biochemical parameters were added to the list of candidate variables, multiple linear regression identified the following additional predictors of [K]: For Patient 1 [TCO_2] ($p < 0.001$) and anion gap ($p < 0.001$); and for Patient 2 [TCO_2] ($p < 0.001$) and $[Na]_{Corr}$ ($p = 0.009$). The coefficient assigned to [Glu] was 0.002 in all multiple linear regression models.

Figure *1* shows the percentages of hyperkalemic episodes associated with hyperglycemia, catabolic illness, and other causes. Pre-HD and HD periods were analyzed separately in each patient. Hyperglycemia and catabolic illness combined accounted for 76.2% to 90.0% of the hyperkalemic episodes. For severe hyperkalemia, hyperglycemia and catabolic illnesses accounted for 84.2% of the hyperkalemic episodes in the pre-HD period of Patient 1 and for 100% of the hyperkalemic episodes in the HD period of Patient 1 and the pre-HD and HD periods of Patient 2.

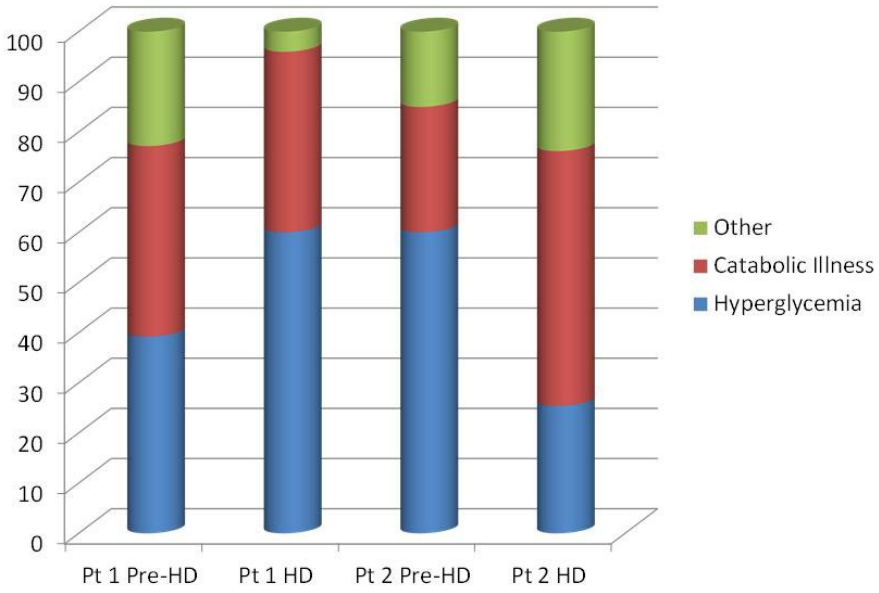

FIGURE 1: Percent of episodes of hyperkalemia (□[K]□_S ≥5.1 mmol/L) associated with severe hyperglycemia, catabolic illness and other causes. Pt = patient. HD = hemodialysis period.

Discussion

The main finding of this report was that the great majority of the episodes of hyperkalemia in both patients were associated with severe hyperglycemia or active catabolic illness. These mechanisms of hyperkalemia were noted during both the pre-HD and HD periods. The hyperkalemic effects of hyperglycemia and catabolic illness are consequences of disturbances in the internal potassium balance. The exit of potassium from cells is reversible by administration of insulin in hyperglycemic hyperkalemia and irreversible when catabolic illness causes cell death.

The hyperglycemic egress of potassium from cells is caused by two interdependent mechanisms. The fundamental hyperkalemic mechanism is absence of insulin [11-14]. Hyperglycemia secondary to insulin deficit causes also hypertonicity secondary to extracellular solute (glucose) gain [14]. Hypertonicity causes exit of potassium from cells [15]. Hypertonicity secondary to hyperglycemia is aggravated in patients with substantial renal function by excessive loss of water through osmotic diuresis [14, 16-17]. Katz's coefficient [9] provides an estimate of the fraction of hypertonicity that is due to extracellular glucose gain. This coefficient estimates that serum tonicity increases by 2.4 mmol/L for each 100 mg/dL rise in [Glu] [14]. The corrected serum sodium concentration [10] uses Katz's coefficient to compute an estimate of the relative loss of water through osmotic diuresis [14]. Osmotic diuresis causes, in addition to excessive water loss, large losses of potassium that counterbalance the exit of potassium from the cells. In the face of large potassium losses in patients with preserved renal function and severe hyperglycemia, [K] may be elevated, in the normal range, or even low [17].

Severe hyperglycemia developing in patients with end-stage renal disease (ESRD) is not associated with large water loss through osmotic diuresis. Consequently, the degree of hypertonicity in dialysis-associated hyperglycemia is predicted by Katz's formula with remarkable accuracy [18]. Urinary potassium losses are also limited, and hyperkalemia is frequent in hyperglycemic episodes occurring in this setting [19-20]. The degree of hyperglycemic hyperkalemia in dialysis patients is higher when ketoacidosis is present [19, 21]. Ketoacidosis contributes to the development of hyperglycemic hyperkalemia by affecting the function of several transport pathways in the cell membrane [22]. Insulin is the only required treatment for both hyperglycemia and hyperkalemia in patients with ESRD, although additional measures may be necessary for extreme cases of hyperkalemia [19-20, 23].

Hyperglycemia was frequent and caused hyperkalemia in both patients of this report during both the pre-HD and HD periods. We addressed the question whether the relationship between [Glu] and [K] differs between the pre-HD and HD periods. There is evidence suggesting that the regulation of internal potassium balance and the effects of insulin on certain aspects of transport across cell membranes differ between the pre-HD and HD periods; therefore, it is possible that the relation between [Glu] and [K] may also differ between these periods. A synopsis of this evidence is presented below.

Investigations of the disruption of cellular functions in uremia suggest that uremic abnormalities of the function of the sodium-potassium ATPase (Na/K-ATPase) of the cell membranes is the root of the uremic defect in cellular potassium uptake. Uremia (circulating uremic factor(s)) was shown to cause a decrease in the activity of the cellular membrane Na/K-ATPase first in red cells [24] and subsequently in several other cell types and tissues, including leukocytes, sarcolemma, and intestines [25-26]. A class of digitalis-like compounds, labelled collectively as endogenous cardiotonic steroids (CTS), has been linked to the uremic inhibition of cell membrane Na/K-ATPase activity. The decrease in this activity leads to decreases in cytosolic potassium [27]. CTS, which have pleiotropic actions, are either cardenolides (endogenous ouabain) or bufadienolides (telocinobufagin, marinobufagenin). In a recent report, marinobufagenin (MBG) was found to be an important inhibitor of the cell membrane Na/K ATPase in uremia [28]. Plasma MBG levels were elevated in both patients with renal failure and experimental animals with renal failure following partial nephrectomy. The elevated plasma MBG levels were associated with decreases in cell membrane Na/K-ATPase activity, which returned toward normal levels after the addition of MBG-binding antibodies [28]. Whether additional molecular mechanisms contribute also to the uremic defect of the internal potassium balance is not clear.

A hemodialysis dose leading to correction of clinical uremic manifestations also corrects the uremic defect in cellular potassium uptake [29]. The effect of dialysis on plasma MBG levels has not been reported thus far, to our knowledge. Uremia also causes peripheral tissue resistance to

the hypoglycemic effect of insulin [30], while the effect of insulin on cellular uptake of potassium is unchanged [31] or enhanced [32] in uremia.

No difference in the relationship between [K] and [Glu] was found between the pre-HD and HD periods in this report. All four linear regressions of [K] on [Glu] found the same regression coefficient (0.002). The regression equations compute that [K] increased by 0.2 mmol/L for each 100 mg/dL rise in [Glu] in both the pre-HD and HD periods in both patients. It is of note that, in addition to the simple regressions, all four multiple regressions assigned the same coefficient (0.002) to the relationship between [Glu] and [K]. The effect of hyperglycemia on [K] was uniform in both patients throughout the observed course of CKD. This finding was robust. However, whether this finding is applicable in general to patients with diabetes mellitus and CKD will need studies in large cohorts of patients. Prevention of severe hyperglycemia in patients who exhibit a hyperkalemic effect of hyperglycemia similar to that found for the two patients in this report will also prevent, to a large extent, severe hyperkalemia.

The highest [K] and [Glu] values were observed in both patients during episodes of diabetic ketoacidosis. Although ketoacidosis was not identified as a predictor of [K], [TCO_2] and serum anion gap, both of which showed their largest deviations from normal values in episodes of ketoacidosis (Tables *2*-*5*), had a significant effect on [K] by multivariable analysis. In addition, [K] values corresponding to the mean [Glu] values calculated from the linear regressions differed minimally from the corresponding actual mean [K] values for the episodes of non-ketotic hyperglycemia (Tables *2*-*3*), but were lower, by 0.36 to 1.15 mmol/L, than the corresponding actual mean [K] values for the episodes of ketoacidosis (Tables *4*-*5*). These findings are consistent with previous findings supporting an added hyperkalemic effect of ketoacidosis in CKD patients [19, 21].

Although the magnitude of hyperkalemia was less in episodes of active catabolic illness than in hyperglycemic episodes, multivariate analysis identified catabolic illness as a predictor of hyperkalemia. Combined, hyperglycemia, and catabolic illness accounted for the majority of the episodes of hyperkalemia (Figure *1*) and almost all the episodes of severe hyperkalemia in both patients.

Conclusions

In addition to bringing to the forefront derangements of internal potassium balance as a cause of hyperkalemia in CKD, the findings of this report also suggest that at least several of these derangements are preventable. The main limitation of the report is that it presents only two patients. The mechanisms of hyperkalemia in CKD patients are multiple and often involve the external potassium balance. Studies in large numbers of patients on chronic dialysis are needed to identify the principal causes of hyperkalemia in dialysis populations. The purpose of this report was to illustrate a method of detailed analysis of all the factors that can potentially cause hyperkalemia in individuals with CKD, including factors related to the internal potassium and external balance. Such an analysis should guide individualization of the preventive measures.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any

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References

1. Liamis G, Rodenburg EM, Hofman A, Zietse R, Stricker BH, Joorn EJ: Electrolyte disorders in community subjects: Prevalence and risk factors. Am J Med. 2013, 126:256-263.
2. Tzamaloukas AH, Glew RH: Recent updates and future perspectives in the treatment of electrolyte disorders. Clinical Practice. 2013, 10:679-682.
3. Einhorn LM, Zhan M, Hsu VD, Walker LD, Moen MF, Seliger SL, Weir MR, Fink JC: The frequency of hyperkalemia and its significance in chronic kidney disease. Arch Intern Med. 2009, 169:1156-1162.
4. Tzamaloukas AH, Avasthi PS: Temporal profile of serum potassium concentration in non-diabetic and diabetic outpatients on chronic dialysis. Am J Nephrol. 1987, 7:101-109.
5. Kleeman CR, Okun R, Heller RJ: The renal regulation of sodium and potassium in patients with chronic renal failure (CRF) and the effect of diuretics on the excretion of these ions. Ann NY Acad Sci. 1966, 139:520-539.
6. Bilbrey GL, Carter NW, White MG, Schilling JF, Knochel JP: Potassium deficiency in chronic renal failure. Kidney Int. 1973, 4:423-430.
7. Kassam H, Sun Y, Adeniyi M, Agaba EI, Martinez M, Servilla KS, Raj DSC, Murata GH, Tzamaloukas AH: Hospitalizations before and after initiation of chronic hemodialysis . Hemodialysis Int. 2011, 15:341-349.
8. McCurdy DK: Hyperosmolar hyperglycemic nonketotic diabetic coma. Med Clin North Am. 1970, 54:683-699.
9. Katz MA: Hyperglycemia-induced hyponatremia: Calculation of the expected sodium depression. NEJM. 1973, 289:843-844.
10. Al-Kudsi RR, Daugirdas JT, Ing TS, Kheirbek AO, Popli S, Hano JE, Gandhi VL: Extreme hyperglycemia in dialysis patients. Clin Nephrol. 1982, 17:228-231.
11. Tzamaloukas AH, Avasthi PS: Serum potassium concentration in hyperglycemia of diabetes mellitus with long-term dialysis. West J Med. 1987, 146:571-575.
12. De Fronzo RA, Sherwin RS, Dillingham M, Hendler R, Tamborlane WV, Felig P: Influence of basal insulin and glucagon secretion on potassium and sodium metabolism. Studies with somatostatin in normal dogs and in normal and diabetic human beings. J Clin Invest. 1978, 61:472-477.

13. Adrogué HJ, Lederer ED, Suki WK, Eknoyan G: Determinants of plasma potassium in diabetic ketoacidosis. Medicine (Baltimore). 1986, 65:163-172.
14. Tzamaloukas AH, Sun Y, Konstantinov NK, Ing TS, Dorin RI, Malhotra D, Murata GH, Shapiro JI: Principles of quantitative fluid and cation replacement in extreme hyperglycemia . Cureus. 2013, 5:3110. http://www.cureus.com/articles/2390-hyperkalemia-in-two-patients-with-diabetes-mellitus-and-chronic-kidney-disease-and-the-role-of-disrupted-internal-potassium-balance#.UxGv_PmwLOY.
15. Moreno M, Murphy C, Goldsmith C: Increase in serum potassium resulting from the administration of hypertonic mannitol and other solutions. J Lab Clin Med. 1969, 73:291-298.
16. Daugirdas JT, Kronfol NO, Tzamaloukas AH, Ing TS: Hyperosmolar coma: Cellular dehydration and the serum sodium concentration. Ann Intern Med. 1989, 110:855-857.
17. Arieff AI, Carroll HJ: Non-ketotic hyperosmolar coma with hyperglycemia: clinical features, pathophysiology, renal function, acid-base balance, plasma-cerebrospinal fluid equilibria and the effects of therapy in 37 cases. Medicine (Baltimore). 1972, 51:73-94.
18. Tzamaloukas AH, Ing TS, Siamopoulos KC, Rohrscheib M, Elisaf MS, Raj DSC, Murata GH: Body fluid abnormalities in severe hyperglycemia in patients on chronic dialysis. Review of published reports. J Diabet Complic. 2008, 22:29-37.
19. Rohrscheib M, Tzamaloukas AH, Ing TS, Siamopoulos KC, Elisaf MS, Murata GH: Serum potassium concentration in hyperglycemia of chronic dialysis. Adv Perit Dial. 2005, 21:102-105.
20. Tzamaloukas AH, Ing TS, Elisaf MS, Raj DSC, Siamopoulos KC, Rohrscheib M, Murata GH: Abnormalities in serum potassium concentration in dialysis-associated hyperglycemia and their correction with insulin: Review of published reports. Int Urol Nephrol. 2011, 43:451-459.
21. Tzamaloukas AH, Ing TS, Elisaf MS, Raj DSC, Siamopoulos KC, Rohrscheib M, Murata GH: Abnormalities in serum potassium concentration in dialysis-associated hyperglycemia and their correction with insulin: A unique clinical/physiologic exercise in internal potassium balance. Int Urol Nephrol. 2010, 42:1015-1022.
22. Aronson PS, Giebisch G: Effects of pH on potassium. New explanations for old observations. J Am Soc Nephrol. 2011, 22:1981-1989.
23. Tzamaloukas AH, Murata GH, Siamopoulos KC, Raj DSC, Elisaf MS, Rohrscheib M, Ing TS: Pathophysiology and management of severe hyperglycemia in patients on chronic dialysis . Semin Dial. 2008, 21:431-439.
24. Welt LG, Sachs JR, McManus TJ: An ion transport defect in erythrocytes from uremic patients . Trans Assoc Am Physicians. 1964, 77:169-181.
25. Kahn T, Thomas K: Na+-K+pump in chronic renal failure. Am J Phsyiol. 1987, 252:F785-F793.
26. Meyer TW, Hostetter TH: Uremia. N Engl J Med. 2007, 357:1316-1324.
27. Bagrov AY, Shapiro JI, Fedorova OV: Endogenous cardiotonic steroids: physiology, pharmacology, and novel therapeutic targets. Pharmacol Rev. 2009, 61:9-38.
28. Kolmakova EV, Haller ST, Kennedy DJ, Isachkina AN, Budny GV, Frolova EV, Pecha G, Nikitina ER, Malhotra D, Fedorova OV, Shapiro JI, Bagrov AY: Endogenous cardiotonic steroids in chronic renal failure. Nephrol Dial Transplant. 2011, 26:2912-19.
29. Cotton JR. Woodard T, Carter NW, Knochel JP: Resting skeletal muscle membrane potential as an index of uremic toxicity. A proposed new method to assess adequacy of hemodialysis. J Clin Invest. 1979, 63:501-506.
30. Tzamaloukas AH, Siamopoulos KC, Raj DSC, Elisaf MS, Ing TS: Glucose homeostasis in patients on chronic dialysis. Dialysis. History Development and Promise. Ing TS, Rathman MA, Kjellstrand K (ed): World Scientific Publishers, 2012. 723-734.
31. Alvestrand A, Wahren J, Smith D, DeFronzo RA: Insulin-mediated potassium uptake is normal in uremic and healthy subjects. Am J Phsyiol. 1984, 246:E174-E180.
32. Goecke IA, Bonilla S, Marusic ET, Alvo M: Enhanced insulin sensitivity in extrarenal potassium handling in uremic rats. Kidney Int. 1991, 39:39-43.