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Prevalence and correlates of hyperkalemia in a renal nutrition clinic

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Abstract
Hyperkalemia (HK) is a frequent complication of chronic kidney disease (CKD). Vegetable-based renal diets are considered at risk due to the high potassium (K) content. The aim of this study was to describe the prevalence and correlates of chronic hyperkalemia (HK) in CKD patients on nutritional care, and in particular, the risk of HK in patients on plant-based versus animal-based low-protein diets. We recruited adult patients affected by CKD not on dialysis, afferent to our renal nutrition clinic from November 2014 to May 2019. We evaluated a total of 870 accesses in 219 patients (172 m, 47 f, age 67 ± 13 years). HK was defined as mild when K serum level was 5.1–5.9 mEq/l, moderate when K serum level was 6.0–6.9 mEq/l, and severe HK when K serum level was ≥ 7 mEq/l. Biochemical, anthropometric data and medications were recorded. The prevalence of HK in all the renal nutrition visits was 26.1%; all but six cases were mild HK, whereas no severe HK was observed. The prevalence of HK was associated with decreased eGFR, up to 36.5% for eGFR < 20 ml/min. Medications were similar in hyperkalemic and normokalemic patients, RAASi being present in up to 85% of patients. In a follow-up of 40 ± 14 months, no association was found between HK and mortality, whereas HK, at the start of follow-up, showed a trend to increased ESRD risk. Serum potassium levels and prevalence of HK were not different between patients on animal-based low-protein diet and plant-based low-protein diet. In conclusion, chronic HK is quite prevalent in a renal nutrition clinic, especially when eGFR falls down below 60 ml/min, thereby reaching the highest prevalence in CKD stage 4. Hyperkalemia is mostly mild, being moderate to severe HK quite infrequent. Hyperkalemia was not associated with higher risk of mortality, whereas a trend, although not statistically significant, was observed for lower ESRD-free survival. Plant-based low-protein diet is not associated with significant higher prevalence of HK with respect to animal-based LPD at the same residual kidney function.

Keywords CKD · Potassium · Hyperkalemia · Renal diets · Nutrition

Introduction

Hyperkalemia is a frequent complication of chronic kidney disease. Abnormalities in the mechanisms of renal excretion, the presence of diabetes or cardiovascular diseases, and medications are the main risk factors for hyperkalemia. Metabolic acidosis, insulin deficiency, and hypertonicity caused by hyperglycemia can alter potassium redistribution, thereby favoring its release into the extracellular space. The use of drugs with cardioprotective and nephroprotective effects, such as renin–angiotensin–aldosterone system inhibitors (RAASi), may favor the increase of potassium levels as well [1, 2].

Hyperkalemia is quite unusual when glomerular filtration rate (GFR) is over 60 ml/min, and in people with preserved GFR, hyperkalemia is commonly associated with a drug-induced impairment of potassium excretion [3]. Several aspects of diagnosis and treatment of chronic hyperkalemia in non-dialysis CKD patients are still on debate [4].

The most recent KDIGO 2019 [5] suggests classifying hyperkalemia by combination of K serum levels and ECG findings: mild (sK 5–5.9 mmol/l without ECG changes), moderate (sK 5.0–5.9 mmol/l with ECG changes or sK 6.0–6.4 mmol/l without ECG changes) or severe (sK 6.0–6.4 mmol/l with ECG changes or sK > 6.5 mmol/l). The American Heart Association [6] proposes the following criteria: mild when sK 5.1–5.9 mmol/l, moderate when sK 6.0–6.9 mmol/l and severe when sK ≥ 7 mmol/l.

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Renal diets are thought to favor the increase of potassium intake as they are based on the principles of a healthy diet that recommends the consumption of vegetables, fruit, nuts, and pulses, all of them being rich in potassium.

The nutritional therapy in CKD aims to reduce the consumption of foods that result in the production of waste substances that patients with kidney failure are no longer able to excrete. Renal diets provide a modification of quantity and quality of dietary protein on the base of patients' residual renal function and clinics. A restriction of protein intake below the recommended daily allowance of 0.8 g/kg/day, for the general population, is strongly suggested to guarantee a good metabolic balance to prevent signs and symptoms of kidney failure and delay the need of dialysis treatment [7]. So, the dietary treatment includes a "low-protein" (0.6–0.7 g/kg/day) diet, characterized by the combination of protein-free products and proteins from animal sources (standard low-protein diet), or the combination of cereals and pulses as sources of vegetable proteins (vegan diet) or a "very low-protein" (0.3–0.4 g/kg/day) diet supplemented with essential amino acids and ketoacids based on the combination of protein-free products and plant-based foods. Plant-based low-protein diets could lead to a potassium load, but the association with some educational strategies, such as favorable cooking methods and a careful selection of food inside the different food groups, helps in reducing potassium load. However, vegetable-based diets have additional beneficial effects. Plant-based foods supply alkali or weak acids contributing to a lower net acid load and a correction of metabolic acidosis, one of the main causes of hyperkalemia. Moreover, they are a source of fibers that have a positive effect on gut microbiota and intestinal motility preventing dysbiosis and constipation, thereby this effect reducing the risk of hyperkalemia as well [8].

Fibers favor the growth of saccharolytic bacteria that produce short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate that have anti-inflammatory properties and protective effects on intestinal barrier and contribute to reduce uremic toxins produced by proteolytic metabolism. The effect of fibers on gut motility is also very important: reduced intestinal motility and constipation are other causes of gut dysbiosis that can contribute to uremic intoxication and increase net absorption of potassium inducing hyperkalemia [9–12].

In this way, vegetarian diets potentially counteract the hyperkalemic effect due to high potassium intake and they did not induce an increase in serum potassium levels in CKD patients. In addition, they have beneficial effects as the reduction of inflammation and oxidative stress [13–16].

Unfortunately, the implementation of renal diets, especially the vegetable-based ones, is limited by the fear of inducing hyperkalemia due to the high proportion of vegetables.

The aim of this study was to describe the prevalence and correlates of hyperkalemia in non-dialysis CKD patients on nutritional care, and particularly in the patients on plant-based versus animal-based low-protein diets.

Patients and methods

This prospective observational study included patients affected by CKD stage I-VND and followed up at our renal nutrition clinic from November 2014 to May 2019, and in which potassium serum levels were available. Patients aged < 18 years, with acute illness, with dialysis commencing within 3 months were excluded. We selected 222 patients, but three were excluded because they assumed intestinal K binders.

Hence, a total of 870 visits in 219 patients (172 males, 47 females, age 67 ± 13 years) were recorded. As comorbidities, we considered a history of diabetes, arterial hypertension, ischemic heart disease, and cerebral and peripheral vascular diseases. Charlson comorbidity index was calculated for all the patients as well.

Table 1 reports some clinical and demographic features of the studied population at baseline distinguished by the presence or absence of HK.

According to AHA classification [6], we assumed as mild HK when K serum level was 5.1–5.9 mEq/l, moderate HK when K serum level was 6.0–6.9 mEq/l, and severe HK when K serum level was ≥ 7 mEq/l. Those patients with at least one detection of sporadic hyperkalemia (HKs) during the follow-up were considered as hyperkalemic.

In all the patients, we assessed BUN, creatinine, glucose, uric acid, sodium, potassium, calcium, phosphorus, bicarbonate, PTH, albumin serum levels and blood cell count; in 24-h urine samples, we assessed creatinine, urea, sodium and total proteins. eGFR was estimated by CKD-EPI equation.

The protein catabolic rate (PCR), as a surrogate of dietary protein intake, was calculated by urea excretion and body weight using the Maroni–Mitch formula [17].

Height was measured with a stadiometer and weight with a mechanical weight scale while patients were wearing light clothes and no shoes; BMI was calculated as weight (kg)/height^2 (m^2). Blood pressure was measured using a digital or aneroid sphygmomanometer, with the patient in sitting position after 15-min rest.

Medications were recorded: ACE inhibitors, angiotensin II receptor blockers, calcium-channel blockers, beta-blockers, alpha-1 inhibitors, vasodilators, loop and thiazide diuretics or aldosterone receptor blockers, phosphate binders, vitamin D preparations, erythropoietin-stimulating agents, and insulin. The use of protein-free products and ketoacid supplementation was also recorded [7, 18].

Table 1 Main clinical characteristic at the time of beginning follow-up of CKD patients without (No-HK) or with hyperkalemia in one assessment at least (HKs)

Factor	HKs $n=101$ (46.1%)	No-HK $n=118$ (53.9%)	p value
Age (years)	68.2 ± 12.5	66.6 ± 12.7	ns
Female, *n* (%)	18 (17.8)	29 (24.6)	ns
Diabetes, *n* (%)	26 (25)	29 (24.6)	ns
Proteinuria, *n* (%)	29 (28.7)	20 (16.9)	< 0.05
Systolic B.P. (mmHg)	139 ± 16	138 ± 15	ns
Diastolic B.P. (mmHg)	81 ± 10	81 ± 11	ns
Heart rate (bpm)	69 ± 11	71 ± 13	ns
eGFR–EPI (ml/min/1.73 m^2)	30.3 ± 14.5	39.0 ± 21.6	< 0.01
BUN (mg/dl)	39 ± 14	32 ± 14	< 0.01
sCreatinine (mg/dl)	2.46 ± 0.99	2.20 ± 1.27	ns
sGlucose (mg/dl)	101 ± 29	104 ± 26	ns
sUric acid (mg/dl)	6.6 ± 3.7	6.2 ± 1.4	ns
sPotassium (mEq/l)	5.0 ± 0.5	4.4 ± 0.4	< 0.01
sSodium (mEq/L)	141 ± 3	140 ± 3	ns
sCalcium (mg/dl)	9.4 ± 0.5	9.4 ± 0.7	ns
sPhosphorus (mg/dl)	3.4 ± 0.5	3.3 ± 0.6	ns
sBicarbonate (mEq/l)	24.1 ± 3.0	25.0 ± 3.1	ns
Haemoglobin (g/dl)	13.0 ± 1.6	13.7 ± 2.4	< 0.05
iPTH (ng/l)	120 ± 82	95 ± 91	ns
sAlbumin (g/dl)	4.1 ± 0.4	4.2 ± 0.4	ns
U creatinine (mg/24 h)	1210 ± 387	1221 ± 353	ns
U urea (g/24 h)	17.2 ± 6.3	19.0 ± 7.0	ns
U sodium (mEq/24 h)	140 ± 55	130 ± 52	ns
Ischemic heart disease, y/n	22/79	19/99	ns
Ictus, y/n	9/92	9/109	ns
Peripheral arteriopathy, y/n	14/87	13/105	ns
Hypertension, y/n	82/12	103/15	ns
Diet types: NPD/LPD/VD, *n*	56/31/12	86/26/8	ns

Data are reported as mean ± SD or absolute frequency (%)

ns not significant, *NPD* normal protein diet, *LPD* animal-based low-protein diet, *VD* plant-based vegetarian low-protein diet

All the patients received personalized dietary counseling, and they were divided into three groups according to the type of renal diet: normal protein (0.8 g/kg/day) diet (NPD), animal-based low-protein (0.6 g/kg/day) diet (LPD), and vegetarian plant-based low protein (0.7 g/kg/day) diet (VD).

After baseline evaluation, patients were followed up for 40 ± 15 months: death for all causes and dialysis start were assumed as end points.

All the patients gave their informed consent to the study which was approved by the ethics committee of the Pisa University Hospital (prot. 66006, del 6.11.2014). All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statistical analysis

The categorical data were described by absolute frequency and percentage, while continuous data were reported as mean ± standard deviation (SD) or median and interquartile range (IQR) when appropriate. Student's *t* test for unpaired data or Mann–Whitney test (when appropriate) was applied to compare quantitative and qualitative variables between groups. The significance of the differences of data expressed as percentage was analyzed using the Chi-square test. A multivariate analysis based on binary logistic regression was successively performed to detect the true significant factors. To compare the type of diet to clinical factors, ANOVA was applied followed by multiple comparisons by Bonferroni method. Pearson's correlation analysis was performed to determine the associations between various selected quantitative parameters. Survival analysis was performed using the Kaplan–Meier method for the events: dialysis start and death for all causes and log-rank test were used to evaluate differences between Kaplan–Meier curves. Cox regressions were performed to calculate Hazard ratio (HR).

Statistical evaluation was carried out with IBM SPSS statistics v.25 (SPSS Inc, Illinois, USA) for Windows. Differences were considered as statistically significant when $p < 0.05$.

Results

Considering the overall access to the renal nutrition clinic, hypokalemia was found in 0.6%, whereas the prevalence of HK was 26.1%. Hyperkalemia was mostly mild, whereas moderate HK occurred in only 0.7% of the visits, and no severe HK was observed.

The prevalence of hyperkalemia increased with the CKD stages. It resulted 4.4% for an eGFR > 60 ml/min, and progressively increased up to 36.4% for eGFR < 20 ml/min 1.73 m^2. CKD stages 1 and 2 were associated with a very low risk of hyperkalemia, which was at the highest prevalence (35.8%) in CKD stage 4. Potassium serum levels and eGFR were negatively associated ($r = -0.246$, $p < 0.001$).

Still considering the overall access to the renal nutrition clinic, the prevalence of HK was similar in animal-based LPD and plant-based VD (33.7 vs 37.9%, $p = 0.40$) regimens.

At the time of beginning of follow-up, hyperkalemia was recorded in 55 out of the 219 patients (25.1%). The

prevalence of diabetes and other comorbidities, was similar in the HKs and the normokalemic patients (Table 1).

Table 1 shows some features of the HK patients at the start of follow-up. They had lower eGFR and hemoglobin, but higher BUN, potassium and prevalence of proteinuria than No-HK. Multivariate analysis showed that proteinuria and the presence of hyperkalemia, at the start of follow-up, were independently associated with the detection of hyperkalemia episodes in the follow-up (Table 2).

As far as medications were concerned, we found no statistical difference in the prevalence of the use of the different classes of drugs between HKs and No-HK. Namely, similar prevalent use of RAASi, calcium-channel blocker, beta-blockers or diuretics was observed in hyperkalemic and no-hyperkalemic patients.

Patients with more preserved kidney function were on NPD (64%), whereas in patients with more advanced kidney insufficiency, LPD was used in 26% of patients and VD was used in 9.5% of cases. The prevalence of HKs was not different among all the types of diet, namely NPD, LPD and VD (Table 1). As expected, LPD and VD patients had a similar residual renal function, but significantly lower than that of patients on NPD (Table 3). No difference was observed in the prevalence of HK or in serum potassium levels between VD and LDP; at baseline, serum potassium was 4.8 ± 0.6 and 4.9 ± 0.5 mEq/l, respectively, and during follow-up, 4.8 ± 0.45 and 4.8 ± 0.4 mEq/l, respectively.

There were no differences between LPD and VD patients in regard to medication use, apart from the tendency to a greater use of vasodilators and diuretics, calcium-channel blockers, and lower use of RAASi in the LPD group. No patient stopped RAASi due to hyperkalemia as well as the LPD or VD. The only measures adopted were a reduction of RAASi dosage and/or dietary counseling.

In the Kaplan–Meier survival analysis, HK patients, at the start of follow-up, showed a trend to increased ESRD risk (Fig. 1), although it was not statistically significant; high levels of eGFR correlated with ESRD-free survival ($p < 0.01$), whereas normokalemia, at the start of follow-up, correlated very weakly ($p = 0.095$) (Table 4). There were no significant differences between no-HK and HK patients regarding mortality for all causes.

Table 2 Multivariate analysis of HK-predictive factors

Factor	RC	OR (95% CI)	*p* value
Proteinuria	0.913	2.492 (1.141–5.441)	0.022
eGFR	0.001	1.001 (0.974–1.027)	0.990
BUN	−0.006	0.994 (0.956–1.033)	0.751
HK at start	4.027	56.1 (15.9; > 100)	< 0.01
Haemoglobin	−0.154	0.858 (0.678–1.084)	0.199

RC regression coefficient, *OR* odds ratio, *95% CI* 95% confidence interval

Discussion

The prevalence of chronic hyperkalemia in our renal nutrition clinic is relevant, approaching 26.1%. It mostly ranks in the range of mild hyperkalemia, while moderate hyperkalemia is a quite limited finding (0.7% of the whole visits) and no severe HK was recorded. Our single-center study reports a lower prevalence of HK than that of a recent larger multicenter study performed in Italy [19]. It is possible that the different classification of HK and the nutritional support we offered may explain, in part at least, the different-prevalence findings.

Hyperkalemia is associated with the decrease of eGFR and higher phosphoremia, more severe secondary hyperparathyroidism, anemia and hypertension (according to the lower residual kidney function). In particular, eGFR lower than 40–30 ml/min represents an important cut-off value under which we have to consider strategies for the prevention of hyperkalemic episodes. Our data show that eGFR lower than 60 ml/min is a crucial factor in the occurrence of hyperkalemia.

The use of RAASi is considered as one of the most frequent causes of hyperkalemia in patients with CKD and, hence, their management is very important. It is well known that with the interruption of RAASi use, the renal- and cardio-protection effects lack.

Medications were similar in hyperkalemic and normokalemic patients, RAASi being present in up to 85% of patients. RAASi therapy is crucial for CKD, diabetes, coronary heart disease, heart failure and hypertension, and its interruption because of hyperkalemia could affect patient's outcome.

Hyperkalemia, at the start of follow-up, was not associated with higher risk of all causes of mortality, whereas a trend, although not statistically significant, was observed for ESRD as the end point. The relationship between hyperkalemia and ESRD is unknown, but it is likely that hyperkalemia could be a risk marker, maybe reflecting comorbidities, drug therapies or a lower level of residual renal function. This is in keeping with the data of Provenzano et al. [19] and De Nicola et al. [20].

Although it is known that acute hyperkalemia can be fatal, the pathophysiological mechanism that can explain the relationship between chronic hyperkalemia and increased mortality is not known [21]. It is noteworthy that the quite low number of patients included in our study may be a limitation for survival analysis.

The management of chronic hyperkalemia represents a major issue in the clinical practice [22]. The interruption of

Table 3 Main features of CKD patients at the time of beginning follow-up by dietary prescription: normal protein diet (NPD), animal-based low-protein diet (LPD) and plant-based vegetarian low-protein diet (VD)

Factor	NPD *n* = 142 (64.4%)	LPD *n* = 57 (26.1%)	VD *n* = 20 (9.5%)
Age (years)	66.6 ± 11.9	70.8 ± 13.3	63.8 ± 14.4
Female, *n* (%)	31 (21.8)	8 (14)	6 (30)
Diabetes, *n* (%)	34 (23.8)	17 (29.3)	4 (19.1)
Proteinuria, *n* (%)	34 (23.8)	8 (13.8)*	7 (33.3)*
Weight (kg)	81.9 ± 14.2	76.5 ± 11.8*	75.4 ± 11.4*
BMI (kg/m^2)	29.0 ± 4.8	26.9 ± 3.2*	27 ± 3.4
Charlson comorbidity index	5.6 ± 1.9	6.7 ± 2.4*	5.8 ± 1.6
HK at start of FU, *n* (%)	21 (14.7)	21 (36.2)	7 (33.3)*
HKs, *n* (%)	52 (36.6)	32 (56.1)*	13 (65.0)*
Systolic BP (mmHg)	139 ± 15	137 ± 17	142 ± 12
Diastolic BP (mmHg)	81 ± 10	79 ± 11	85 ± 14
Heart rate (bpm)	70 ± 12	69 ± 13	73 ± 10
eGFR-EPI (ml/min/1.73 m^2)	42.8 ± 18.4	20.5 ± 10.2**	22.9 ± 11.7**
BUN (mg/dl)	32 ± 12	44 ± 13*	43 ± 17*
Creatinine (mg/dl)	1.8 ± 0.6	3.4 ± 1.3*	3.1 ± 1.1*
Glucose (mg/dl)	102 ± 26	105 ± 30	92 ± 24
Uric acid (mg/dl)	6.4 ± 3.2	6.6 ± 1.8	5.6 ± 1.2
Sodium (mEq/l)	139 ± 11	141 ± 3	142 ± 3
Potassium (mEq/l)	4.6 ± 0.5	4.9 ± 0.5*	4.8 ± 0.6
Calcium (mg/dl)	9.4 ± 0.4	9.3 ± 0.5*	9.0 ± 0.7^
Phosphorus (mg/dl)	3.2 ± 0.5	3.6 ± 0.6*	3.6 ± 0.6*
Bicarbonate (mEq/l)	25.1 ± 3.2	23.7 ± 2.9*	24.3 ± 2.9
Haemoglobin (g/dl)	13.9 ± 2.2	12.5 ± 1.5*	12.6 ± 1.5*
iPTH (ng/l)	81 ± 58	161 ± 120*	128 ± 77*
Albumin (g/dl)	4.2 ± 0.4	4.1 ± 0.3	4.1 ± 0.4
U creatinine (mg/24 h)	1245 ± 365	1165 ± 373	1171 ± 391
U urea (g/24 h)	20.1 ± 6.4	13.4 ± 5.4*	15.8 ± 6.7*
U sodium (mEq/24 h)	136 ± 56	128 ± 51	126 ± 59
PCR (g/24 h)	74.2 ± 19.0	54.2 ± 17.6*	61.2 ± 20.0*
nPCR (g/Kg p.c./24 h)	0.90 ± 0.22	0.68 ± 0.15*	0.79 ± 0.23

Data are reported as mean ± SD or absolute frequency (%)

BP blood pressure, *eGFR-EPI* glomerular filtrate value using CKD-EPI formula, *PCR* protein catabolic rate, *nPCR* protein catabolic rate normalized by body weight

**$p < 0.01$; *$p < 0.05$ vs NPD; ^$p < 0.05$ vs LPD, in the multiple comparisons (by Bonferroni method)

RAASi therapy in patients with severe or recurrent hyperkalemia leads to the loss of their cardio- and nephro-protection that could be the cause of the increased risk of dialysis start in these categories.

Serum potassium levels were not influenced by renal diets. In particular, serum potassium levels and prevalence of hyperkalemia were not different between patients with LPD and vegan diet. Similar to RAASi, dietary therapy is very important in the management of CKD patients.

Renal diets, namely low-protein diets, are implemented to protect residual renal function, correct metabolic and hormonal abnormalities and to delay the need for dialysis [7] while preserving nutritional status. Vegetable-based diets are considered "at risk" because of the high potassium content of fruit, vegetables and pulses, but this thought is changing due to the positive effects of plant-based diets. They prevent/improve gut dysbiosis favoring the growth of saccharolytic bacterial species and reducing the proteolytic uremic toxin production. They are a source of fibers that are substrates of saccharolytic bacterial metabolism resulting in short-chain fatty acid production which have an anti-inflammatory effect and exerts a protective action on intestinal barrier. Moreover, they prevent constipation, a potential cause of hyperkalemia; plant-based diets are a source of alkali that counteract metabolic acidosis, another determinant of high potassium levels [9, 10, 12, 16].

As mentioned above, educational strategies help in the management of potassium intake in CKD patients who show

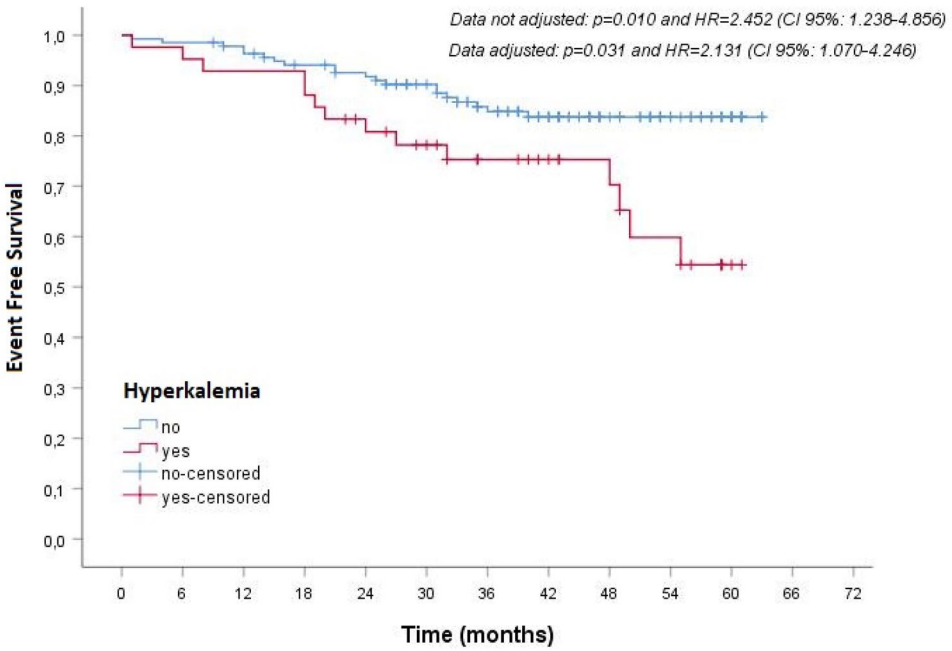

Fig. 1 Kaplan–Meier survival analysis for ESRD according to the serum potassium at the time of beginning of follow-up

Table 4 Multivariate analysis (Cox model) of ESRD-free survival factors

Factor	RC	HR (95% CI)	*p* value
Proteinuria	0.105	1.111 (0.426–2.896)	0.830
eGFR	−0.212	0.809 (0.744–0.879)	<0.01
BUN	0.030	1.030 (0.994–1.068)	0.100
HK at start	0.464	1.490 (0.891–3.198)	0.095
Haemoglobin	−0.049	0.953 (0.692–1.311)	0.766

RC regression coefficient, *HR* hazard ratio, *95% CI* 95% confidence interval

recurrent hyperkaliemia events. The nutritional intervention in CKD is quite complex as it includes the manipulation of protein quantity and quality, a restriction of salt and phosphorus, and an adequate energy supply. So, a targeted nutritional intervention should be performed. Such an intervention is not so easy to realize in the daily clinical practice as it needs time, economic resources and dedicated health professionals, possibly well trained [6, 10].

Foods can be selected based on the potassium content expressed in mg/100 g food, or per serving, or even as a potassium/fiber or potassium/protein ratio [10]. Preparation and cooking techniques can help to modify the potassium content to allow the consumption of foods that would otherwise be excluded. An example is to peel and cut the vegetables into pieces and then boil them; these preparation techniques can alter the taste, the appearance and the nutritional properties of foods, but adding appropriate instructions on how to treat them after boiling (stir-fry, adding spices and herbs), it is possible to get appetizing dishes. These techniques preserve fibers and alkali content [10]. For fruit or vegetables that cannot be prepared in this way, it is possible to provide information on the amount and the frequency of consumption [8, 23].

It is important to pay attention to the hidden sources of potassium, such as salt substitutes or potassium-based preservatives. Salt substitutes are often recommended for hypertensive patients to reduce sodium chloride consumption, but in patients with advanced CKD, they can induce a potassium load. Moreover, it often happens that patients consider them harmless or even healthy and use them even in larger amounts.

With regard to potassium-based preservatives, the effect of their use is still unclear as the scientific literature on this topic is quite poor. Sherman and Mehta, for example, found that enhanced meat and poultry products had potassium levels up to threefold greater than similar unenhanced food products [24].

In any case, it is mandatory to educate patients to read the ingredient list on the nutritional labels to verify the presence or not of potassium-based preservatives, even if it is not possible to know the real amount as the manufacturers are not obliged to reveal it.

The use of educational tools, such as brochures with images and colors, can be helpful in summarizing the essential aspects of dietary potassium control in CKD patients [10, 23].

Since HK poses a clinically relevant risk of life-threatening arrhythmias, the occurrence and persistence of chronic HK in CKD patients represent the condition needing the lowering of dose or withdrawal of RAASi or limiting dietary potassium load [25, 26]. In the last year, two

new potassium-intestinal binders have been approved by FDA and EMA for the treatment of chronic hyperkalemia. Namely, patiromer and sodium–zirconium cyclosilate are both effective and well tolerated in studies on patients with chronic hyperkalemia and in RAASi therapy [27–31].

The main limitation of the study is the single center, prospective observational design, and the quite low number of patients recruited.

In conclusion, chronic HK is quite prevalent in a renal nutrition clinic, especially when eGFR falls down to 60 ml/min, reaching the highest prevalence in stage 4. However, hyperkalemia is mostly mild, being moderate to severe HK quite infrequently. Hyperkalemia was not associated with higher risk of mortality, whereas a trend, although not statistically significant, was observed for lower ESRD-free survival. Plant-based low-protein diet is not significantly associated with higher prevalence of HK with respect to animal-based LPD at the same residual kidney function.

Author contribution AdC made substantial contribution to conception and design, drafting and revising the manuscript critically for important intellectual content; CDA contributed to drafting and editing the manuscript for important intellectual content; AC, EP contributed to data collection; PS, CM contributed to drafting the manuscript; RM performed statistical analysis.

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Compliance with ethical standards

Conflict of interest AdC received consulting fees from Dr Shaer, Shire, Vifor Pharma, Fresenius Kabi; CDA received consulting fees from Baxter and Dr Shaer.

Statement of human and animal rights All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent All the patients gave their informed consent to the study which was approved by the ethics committee of the Pisa University Hospital (prot. 66006, del 6.11.2014).

References

1. Kovesdy CP (2015) Management of hyperkalemia: an update for the internist. Am J Med 128:1281–1287
2. Palmer BF (2004) Managing hyperkalemia caused by inhibitors of the renin–angiotensin–aldosterone system. N Engl J Med 351:585–592
3. Pecoits-Filho R, Fliser D, Tu C, Zee J, Bieber B, Wong MMY, Port F, Combe C, Lopes AA, Reichel H, Narita I, Stengel B, Robinson BM, Massy Z, CKDopps Investigators (2019) Prescription of renin-angiotensin-aldosterone system inhibitors (RAASi) and its determinants in patients with advanced CKD under nephrologist care. J Clin Hypertens (Greenwich) 21:991–1001
4. De Nicola L, Di Lullo L, Paoletti E, Cupisti A, Bianchi S (2018) Chronic hyperkalemia in non-dialysis CKD: controversial issues in nephrology practice. J Nephrol 31(5):653–664
5. Clase CM, Carrero JJ, Ellison DH, Grams ME, Hemmelgarn BR, Jardine MJ, Kovesdy CP, Kline GA, Lindner G, Obrador GT, Palmer BF, Cheung M, Wheeler DC, Winkelmayer WC, Pecoits-Filho R, Conference Participants (2020) Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 97(1):42–61
6. Vanden Hoek TL, Morrison LJ, Shuster M et al (2010) Part 12: cardiac arrest in special situations: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 122:S829–861
7. Cupisti A, Brunori G, Di Iorio BR, D'Alessandro C, Pasticci F, Cosola C, Bellizzi V, Bolasco P, Capitanini A, Fantuzzi AL, Gennari A, Piccoli GB, Quintaliani G, Salomone M, Sandrini M, Santoro D, Babini P, Fiaccadori E, Gambaro G, Garibotto G, Gregorini M, Mandreoli M, Minutolo R, Cancarini G, Conte G, Locatelli F, Gesualdo L (2018) Nutritional treatment of advanced CKD: twenty consensus statements. J Nephrol 31(4):457–473. https://doi.org/10.1007/s40620-018-0497-z**Epub 2018 May 24**
8. Cupisti A, D'Alessandro C, Gesualdo L, Cosola C, Gallieni M, Egidi MF, Fusaro M (2017) Non-traditional aspects of renal diets: focus on fiber, alkali and vitamin K1 intake. Nutrients 9:444
9. Slavin J (2013) Fiber and prebiotics: mechanisms and health benefits. Nutrients 5:1417–1435
10. Cupisti A, Kovesdy CP, D'Alessandro C, Kalantar-Zadeh K (2018) Dietary approach to recurrent or chronic hyperkalaemia in patients with decreased kidney function. Nutrients 10:261. https://doi.org/10.3390/nu10030261
11. St-Jules DE, Goldfarb DS, Sevick MA (2016) Nutrient non-equivalence: does restricting high-potassium plant foods help to prevent hyperkalemia in hemodialysis patients? J Ren Nutr 26(5):282–287. https://doi.org/10.1053/j.jrn.2016.02.005
12. Camerotto C, Cupisti A, D'Alessandro C, Muzio F, Gallieni M (2019) Dietary fiber and gut microbiota in renal diets. Nutrients. https://doi.org/10.3390/nu11092149
13. Barsotti G, Morelli E, Cupisti A, Meola M, Dani L, Giovannetti S (1996) A low-nitrogen low-phosphorus vegan diet for patients with chronic renal failure. Nephron 74:390–394
14. Cupisti A, Morelli E, Meola M, Barsotti M, Barsotti G (2002) Vegetarian diet alternated with conventional low-protein diet for patients with chronic renal failure. J Ren Nutr 12:32–37
15. Di Iorio BR, Di Micco L, Marzocco S, De Simone E, De Blasio A, Sirico ML, Nardone L, On Behalf Of Ubi Study Group (2017) Very Low-protein Diet (VLPD) reduces metabolic acidosis in subjects with chronic kidney disease: the "Nutritional Light Signal" of the RenalAcid Load. Nutrients 17:69
16. Cases A, Cigarrán-Guldrís S, Mas S, Gonzalez-Parra E (2019) Vegetable-based diets for chronic kidney disease? It is time to reconsider. Nutrients. https://doi.org/10.3390/nu11061263
17. Maroni BJ, Steinman TI, Mitch WE (1985) A method for estimating nitrogen intake in patients with chronic renal failure. Kidney Int 27:58–65
18. D'Alessandro C, Rossi A, Innocenti M, Ricchiuti G, Bozzoli L, Sbragia G, Meola M, Cupisti A (2003) Dietary protein restriction for renal patients: don't forget protein-free foods. J Ren Nutr 23(5):367–371
19. Provenzano M, Minutolo R, Chiodini P et al (2018) Competing risk analysis of death and end stage kidney disease by hyperkalaemia status in non-dialysis chronic kidney disease patients receiving stable nephrology care. J Clin Med 7(12):E499. https://doi.org/10.3390/jcm7120499
20. De Nicola L, Donfrancesco C, Minutolo R, Lo Noce C, Palmieri L, De Curtis A, Iacoviello L, Zoccali C, Gesualdo L, Conte G,

Vanuzzo D, Giampaoli S, ANMCO-SIN Research Group (2015) Prevalence and cardiovascular risk profile of chronic kidney disease in Italy: results of the 2008–2012 National Health Examination Survey. Nephrol Dial Transplant 30(5):806–814
21. Collins AJ, Pitt B, Reaven N, Funk S, McGaughey K, Wilson D, Bushinsky DA (2017) Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. Am J Nephrol 46(3):213–221. https://doi.org/10.1159/000479802
22. Rossignol P, Ruilope LM, Cupisti A, Markus Ketteler M, Wheeler DC, Pignot M, Cornea G, Schulmann T, Lund LH (2019) Recurrent hyperkalaemia management and use of renin–angiotensin–aldosterone system inhibitors: a European multi-national targeted chart review. Clin Kidney J. https://doi.org/10.1093/ckj/sfz129
23. D'Alessandro C, Piccoli GB, Calella P, Brunori G, Pasticci F, Egidi MF, Capizzi I, Bellizzi V, Cupisti A (2016) "Dietaly": practical issues for the nutritional management of CKD patients in Italy. BMC Nephrol 17(1):102. https://doi.org/10.1186/s12882-016-0296-5
24. Sherman RA, Mehta O (2009) Phosphorus and potassium content of enhanced meat and poultry products: implications for patients who receive dialysis. Clin J Am Soc Nephrol 4(8):1370–1373. https://doi.org/10.2215/CJN.02830409
25. Bianchi S, Aucella F, De Nicola L, Genovesi S, Paoletti E, Regolisti G (2019) Management of hyperkalemia in patients with kidney disease: a position paper endorsed by the Italian Society of Nephrology. J Nephrol 32(4):499–516
26. Bianchi S, Regolisti G (2019) Pivotal clinical trials, meta-analyses and current guidelines in the treatment of hyperkalemia. Nephrol Dial Transplant 34(Suppl 3):iii51–iii61. https://doi.org/10.1093/ndt/gfz213
27. Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, Wittes J, Christ-Schmidt H, Berman L, Pitt B, OPAL-HK Investigators (2015) Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med 372:211–221
28. Weir MR, Bushinsky DA, Benton WW, Woods SD, Mayo MR, Arthur SP, Pitt B, Bakris GL (2018) Effect of patiromer on hyperkalemia recurrence in older chronic kidney disease patients taking RAAS inhibitors. Am J Med 131:555–564.e3 **(79)**
29. Pitt B, Bakris GL, Weir MR, Freeman MW, Lainscak M, Mayo MR, Garza D, Zawadzki R, Berman L, Bushinsky DA (2018) Long-term effects of patiromer for hyperkalaemia treatment in patients with mild heart failure and diabetic nephropathy on angiotensin-converting enzymes/angiotensin receptor blockers: results from AMETHYST-DN. ESC Heart Fail 5:592–602
30. Packham DK, Rasmussen HS, Lavin PT, El-Shahawy MA, Roger SD, Block G, Qunibi W, Pergola P, Singh B (2015) Sodium zirconium cyclosilicate in hyperkalemia. N Engl J Med 372:222–231
31. Vijayakumar S, Butler J, Bakris GL (2019) Barriers to guideline mandated renin–angiotensin inhibitor use: focus on hyperkalaemia. Eur Heart J Suppl 21(Suppl A):20–27