International Journal of Nephrology and Kidney Failure
ISSN 2380-5498 | Open Access

RESEARCH ARTICLE Volume 10 - Issue 2

Hyperkalemia in Patients with Chronic Kidney Disease Managed with and without Dialysis

Antonio Méndez Durán[1,*], Juan Daniel Díaz García[2], Ivonne Reyes Sánchez[3], Diana Carolina Sánchez Guerrero[4], Ramón Ruíz Mejía[5], Carlos Alberto Bello Soto[6], José Horacio Cano Cervantes[7], Socorro Méndez Balcázar[8], Francisco Fabián Rodríguez[9], Luz Elena Vázquez Martínez[10], Emerson Joachín Sánchez[11], Gabriel Yáñez Boy[11], Imelda López Pérez[12], and Alejandra Rivas Vera[13]

[1]Unidad de Planeación e Innovación en Salud, Instituto Mexicano del Seguro Social, Ciudad de México, México
[2]Servicio de Nefrología y Unidad de Trasplante Renal, Centro Médico Nacional 20 de Noviembre, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Ciudad de México, México
[3]Coordinación Técnica de Servicios Médicos Indirectos, Instituto Mexicano del Seguro Social, Ciudad de México, México
[4]Hospital Christus Muguerza Alta Especialidad, Monterrey, Nuevo León, México
[5]Centro Médico ISSEMYM, Lic, Arturo Montiel Rojas, Toluca, Estado de México, México
[6]Servicio de Nefrología del Hospital General Regional No 25, Instituto Mexicano del Seguro Social, Ciudad de México, México
[7]Servicio de Nefrología y Unidad de Trasplante Renal, Centro Médico Nacional 20 de Noviembre, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Ciudad de México, México
[8]Servicio de Medicina Interna del Hospital General "José María Morelos y Pavón", Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Ciudad de México, México
[9]Servicio de Urgencias del Hospital General de Zona No. 8, Instituto Mexicano del Seguro Social, Uruapan, Michoacán, México
[10]Hospital General de Zona No 50, Instituto Mexicano del Seguro Social, San Luis Potosí, México
[11]AstraZeneca Medical Affairs, México City, México
[12]Hospital General de Zona No 27, Instituto Mexicano del Seguro Social, Ciudad de México, México.
[13]Hospital General de Zona No 197, Instituto Mexicano del Seguro Social, Texcoco de Mora, Estado de México, México

***Corresponding author:** Antonio Méndez Durán, Félix Cuevas Av. No. 301 Interior 207. Col. Del Valle Sur, Alcaldía Benito Juárez, Ciudad de México, México, Tel: 55 14 91 50 31; E-mail: amd740522@hotmail.com

Received: 23 Nov, 2024 | **Accepted:** 04 Dec, 2024 | **Published:** 12 Dec, 2024

Citation: Durán AM, Díaz García JD, Sánchez IR, Sánchez Guerrero DC, Mejía RR, et al. (2024) Hyperkalemia in Patients with Chronic Kidney Disease Managed with and Without Dialysis. Int J Nephrol Kidney Fail 10(2): dx.doi.org/10.16966/2380-5498.247

Abstract

Introduction: Hyperkalemia is commonly asymptomatic in chronic kidney disease (CKD), with the result that not taking it into account continues to be fatal. The main objective was to determine the frequency of hyperkalemia in patients with and without dialysis in Mexico.

Materials and methods: We performed an observational study over a period of 3 months. Data were collected from patients with CKD G1 to 5 not managed with dialysis (Group I), with peritoneal dialysis (Group II), and hemodialysis (Group III). We recorded gender, age, glomerular filtration rate, daily medication intake, and electrocardiographic manifestations. Hyperkalemia was classified as mild (5.6 to 6.5 mEq/L), moderate (6.6 to 7.5 mEq/L), and severe (>7.5 mEq/L). The exclusion criteria were age <18 years, having undergone blood transfusion in the previous 5 days, injury, and acute kidney failure.

Results: The study population comprised 634 patients from 10 sites (4 private and 6 public), 238 in Group I, 188 in Group II, and 208 in Group III (293 females [46.2%]; 341 males (53.8%); mean age 56.2 ± 14.9 years). We recorded diabetes in 100 patients (15.7%), arterial hypertension in 192 (30.2%), diabetes + arterial hypertension in 254 (40.0%), chronic glomerular disease in 25 (3.9%), tubulointerstitial kidney disease in 39 (6.1%), and other conditions in 24 (3.8%). Serum creatinine was 7.1 ± 4.9 mg/dL and potassium 5.6 ± 0.9 mEq/L. Hyperkalemia was detected in 384 patients (61%), mild in 138 (21.7%), moderate in 137 (21.6%), and severe in 109 (17.2%). Fifteen patients (2.3%) had hypokalemia (95% CI, r=0.50-0.81). Electrocardiographic changes were detected in 71 patients (11.1%).

Conclusions: The frequency of hyperkalemia was high. The potential effects of the condition should not be underestimated, independently of electrocardiographic changes.

Keywords: Hyperkalemia; Serum potassium; Chronic kidney disease; Dialysis; Mexico

Introduction

Hyperkalemia (HPK) is a common electrolytic disorder in chronic kidney disease (CKD) that is directly associated with loss of glomerular filtration. Frequency varies with the type of patient under study, the treatment administered, and the chosen reference values for serum potassium. Treatment of HPK is challenging because of its generally asymptomatic course, which hampers detection of the condition and proves challenging when selecting therapy [1-3]. Increased serum potassium values are not directly associated with clinical and electrocardiographic manifestations, although higher values necessitate initiation of treatment owing to the potential onset of arrhythmia, muscle weakness, and cardiac arrest [4-6]. While HPK usually progresses with a transtubular potassium gradient of 10 mL/min, this pathophysiologic principle is modified by extrinsic factors, with the condition found in stages 3 and 4, where diet is key [7,8]. The prevalence of HPK (defined as >5 mEq/L) affects 1.5% of the general population, 5.6% of those taking angiotensin II receptor antagonists (ARAII), and 19% of those with >5.5 mEq/L, a ventricular fraction of <35%, and therapy with spironolactone. Potassium values vary by country depending on the established cut-off. In Switzerland, with a cut-off of >4.7 mEq/L, the prevalence of HPK was 8.8%; in the United States of America, with a cut-off of >5.0 mEq/L, it was 3.6%. In patients with grade 4 disease in the United States of America, prevalence was 1.8%, and in Italy it was 4-5%; in patients undergoing dialysis 2-28%, and in emergency departments, 3-13% [9,10]. Given the heterogeneity of reported results, the main objective was to determine the frequency of hyperkalemia in patients with and without dialysis in Mexico.

Methods

Type of study and setting

We performed an observational study in six clinical units public: Nephrology Service and Kidney Transplant Unit, National Medical Center November 20, Mexico City; Internal Medicine Service of the "José María Morelos and Pavón" General Hospital, both from the Institute of Security and Social Services of State Workers, México City. ISSEMYM Medical Center, Lic. Arturo Montiel Rojas, Toluca, State of México. Emergency Service of the General Hospital of Zone No. 8 Uruapan, Michoacán; General Hospital of Zone No. 50 San Luis Potosí; General Hospital of Zone No. 197, Texcoco de Mora, State of México; all belonging to the Mexican Social Security Institute, Mexico; and four private sectors: Christus Muguerza Alta Especialidad Hospital, Monterrey, Nuevo León; SANEFRO Guadalajara Dialysis Center; Private Hemodialysis Units. México City.

Data source

Data were gathering retrospectively over 3 months from records of outpatients who attended for care. Based on random balanced sampling, 50% of records were collected from the public sector and 50% from the private sector. We identified three groups of patients, the Group I: patients with CKD G1 to G5 (no dialysis), G1 (<90 ml/min), G2 (60-89 ml/min), G3 (30-59 ml/min), G4 (15-29 ml/min) and G5 (<15ml/min); patients undergoing peritoneal dialysis (Group II); and patients undergoing hemodialysis (Group III).

Inclusion criteria

We included patients of any degree of CKD diagnosed based on the serum creatinine value (mg/dL), the estimation of glomerular filtration rate (eGFR) was carried out using the MDRD equation (Modification of Diet in Renal Disease) from the digital platform of the Spanish Society of Nephrology. Patients also had to be on outpatient treatment (4 bags of dialysate solution of 2 litres each, performing 3 short daytime exchanges and 1 long night exchange) or automated peritoneal dialysis with 2 bags of dialysate solution of 6 litres each for nocturnal or conventional hemodialysis and 3 hours of treatment days a week. The duration had to be at least 3 months in both cases.

Exclusion criteria

The exclusion criteria were age <18 years, transfusion during the previous 5 days, injury, acute kidney failure, and hypokalemia (<3.5 mEq/L).

Elimination criteria

Patients with incomplete clinical records were eliminated from the study sample.

Variables

We recorded gender (male and female), age ≥ 18 years, GFR (Group I), and cause of CKD (diabetes mellitus and/or arterial hypertension, chronic glomerular disease, tubulointerstitial kidney disease, other). The primary diagnosis was that recorded by the physician. We also recorded type of replacement therapy (peritoneal dialysis or hemodialysis), daily medication, and electrocardiographic changes. The electrocardiogram was interpreted by the internist, nephrologists or specialist in emergency medicine.

Definitions

Hyperkalemia was defined as increased serum potassium >5.5 mEq/L and categorized as mild (5.6 to 6.5 mEq/L), moderate (6.6 to 7.5 mEq/L) and severe (>7.5 mEq/L).

Associated medication comprised drugs associated with and used directly according to the potassium value, as follows: angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor antagonist (ARA II). calcium antagonists, alpha-blockers, beta-blockers, sodium glucose cotransporter 2 inhibitors (iSGLT-2), aldosterone antagonists, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Statistical analysis

The gathered data about the three different study groups were analyzed with the statistical program SPSS (Statistical Package for the Social Sciences) V. 21, descriptive measurements were applied and we got averages, limits and standard deviation. It is applied the difference between two independent averages (IC 95%), t of Student, taking into account a value of <0.05 for statistical significance. The demographic and biochemical variables are identified by groups, The HPK frequency is presented in a sector graphic. In the group one non-dialysis is correlated with the glomerular filtration rate and the serum potassium value by the coefficient of relationship of Pearson.

Results

We initially assessed 1,283 patients, of whom 649 were eliminated. We included 634 patients. Group I comprised 238 patients, Group II, 188 patients, and Group III, 208 patients (female, 293 [46.2%]; male, 341 [53.8%]; age 56.2 ± 14.9 years (limits 19-92). In the total of 634 patients in the study, diabetes mellitus was found in 100 patients (15.7%), arterial hypertension in 192 (30.2%), diabetes plus arterial hypertension in 254 (40.0%), chronic glomerular disease in 25 (3.9%), tubulointerstitial kidney disease in 39(6.1%), and other conditions in 24 (3.8%). In relation to drugs, ACEi and ARAII were prescribed in 434 (68.4%) cases, NSAIDs in 139 (21.9%), beta-blockers in 124 (19.5%), calcium antagonists in 327(51.5%), diuretics in 248 (39.1%), iSGLT-2

in 87 (13.8%), and aldosterone antagonists in 101 (15.9%) (Table 1). HPK was detected in 384 patients (61%). This was mild in 138 (21.7%), moderate in 137 (21.6%), and severe in 109 (17.2%). Hypokalemia was recorded in 15 patients (2.3%), 8 from Group I and 7 from Group II (Figure 1). Serum potassium values were 5.6+0.9 mEq/L (95% CI, r=0.50) in Group I, 5.8+0.5 mEq/L (95% CI, r=0.81) in Group II, and 5.7+0.9 mEq/L (95% CI, r=0.70) in Group III, eGFR was 22.3+21.2 mL/min in Group I. Potassium values by CKD grade were as follows: stage 1, 4.2+0.8; stage 2, 4.7+0.9; stage 3, 4.8+0.9; stage 4, 5.2+0.9; and stage 5, 5.7+0.9 (95%CI, r=0.50) (Figure 2). No differences were detected for frequency of HPK associated with diuretics (Table 2). Electrocardiographic changes were observed in 71 patients (11.1%), with a symmetrical pointed T wave in 56 cases (78% [3 from Group I, 49 from Group II, and 4 from Group III]) and prolonged PR interval with a pointed T wave in 15 (21.1% [0 in Group I, 14 in Group II, and 1 in Group III; 95% CI, r=0.45). No cases were found with serious arrhythmias or heart blocks that required specialized management.

Discussion

Hyperkalemia was present in all 3 groups at a higher frequency than that reported in the literature. Group I potassium values were weakly correlated with eGFR; in the case of Groups II and III, the correlation was strong. Nevertheless, the differences were not statistically significant. No clinical manifestations were identified. Data on North American patients undergoing peritoneal dialysis show the frequency of HPK to be 14% and that of hypokalemia to be 5%, with the most important factors being a potassium-rich diet, nonadherence to dialysis, increased muscle mass, and changes in daytime potassium values when not on dialysis (in the case of automated dialysis). Values at 3 years remained unchanged [11]. A Chinese multicenter study of 12,000 patients undergoing peritoneal dialysis and hemodialysis found a frequency of 20.7%, the factors most closely associated with a higher grade of hyperkalemia were hemodialysis, diabetes mellitus, higher body mass index, high serum albumin and phosphorus, and low levels of bicarbonate, creatinine, and triglycerides [12]. The increased cardiovascular risk in CKD entails the use of renin-angiotensin-aldosterone system blockers, whose own mechanism of action contributes to increased potassium values. These drugs have been shown to modify the prognosis of cardiovascular conditions and have proven beneficial in cases of heart failure. With the advent

Table 1: Characteristics of patients by study groups.

Variable	Group I CKD (%) n=238	Group II Peritoneal dialysis (%) n=188	Group III Hemodialysis (%) n=208
Gender, n=634			
Female, 293 (46.2%)	110 (46.2)	89 (47.3)	94 (45.2)
Male, 341 (53.8%)	128 (53.8)	99 (52.7)	114 (54.8)
Age			
Mean 56.2 ± 14.9	57.4 ± 15.3	58.6 ± 10.3	52.5 ± 14.8
Limits (19-92)	22-92	25-85	19-89
Etiology of CKD			
Diabetes mellitus	46 (19.3)	40 (21.3)	14 (6.7)
Arterial hypertension	61 (25.6)	35 (18.5)	96 (46.1)
Diabetes plus arterial hypertension	58 (24.3)	109 (58)	87 (41.8)
Chronic glomerular disease	17 (7.1)	0	8 (3.8)
Tubulointerstitial kidney disease	38 (15.9	0	1 (0.5)
Other	18 (7.5)	4 (2.1)	2 (0.5)
Creatinine (mg/dL)			
Mean 7.1 ± 4.9	5.7 ± 3.5	8.1 ± 5.3	7.3 ± 2.3
Limits: 1.3-9.6	-	-	-
Blood glucose (mg/dL)			
Limits: 74-271mg/dL	113 ± 43.3	-	-
Medication			
ACEi or ARAII, 434 (68.4%)	133 (55.9)	164 (87.2)	137 (65.8)
NSAID, 139 (21.9%)	11 (4.6)	61 (32.4)	67 (32.2)
Beta-blocker, 124 (19.5%)	56 (23.5)	31 (16.5)	37 (17.7)
Calcium antagonist, 327 (51.5%)	111 (46.6)	97 (51.5)	119 (57.2)
Diuretic, 248 (39.1%)	65 (27.3)	114 (60.6)	69 (33.1)
iSGLT-2, 87 (13.8%)	22 (9.2)	36 (19.1)	29 (13.9)
Aldosterone antagonist, 101 (15.9%)	3 (1.2)	93 (49.4)	5 (2.4)

CKD: Chronic Kidney Disease; GFR: Glomerular Filtration Rate; ACEi: Angiotensin-Converting Enzyme Inhibitor; ARAII: Angiotensin II Receptor Antagonist; NSAID: Nonsteroidal Anti-Inflammatory Drug; iSGLT-2: Sodium-Glucose Cotransporter 2 Inhibitor.

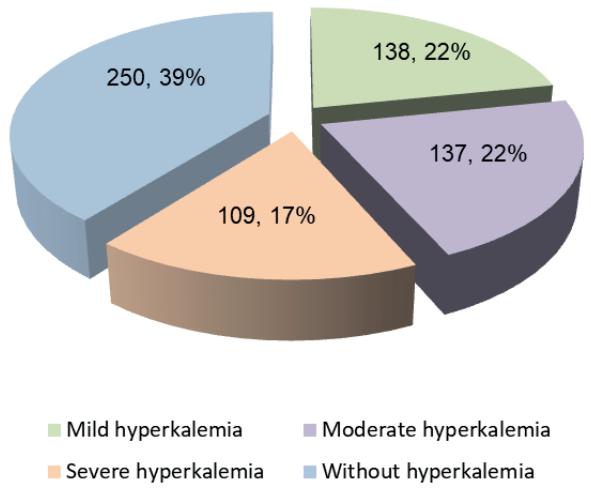

Figure 1: Grades of hyperkalemia (all groups) n=634.

Without hyperkalemia; mild hyperkalemia: >5.5 to 6.4 mEq/L; moderate hyperkalemia: 6.5 to 7.5 mEq/L; severe hyperkalemia: >7.5 mEq/dL.

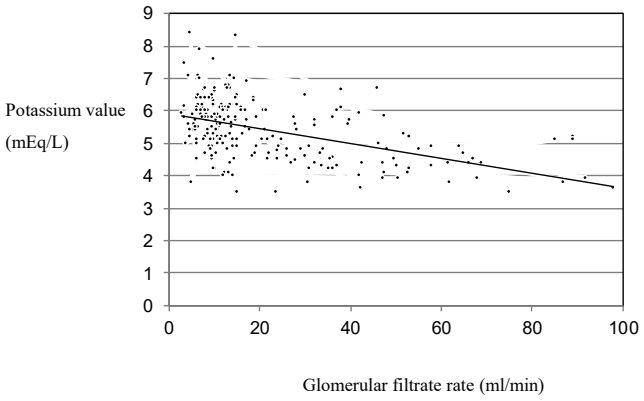

Figure 2: Grades of hyperkalemia (all groups) n=634.

Table 2: Frequency of diuretic-associated hyperkalemia (N=349).

Medication	Group I	Group II	Group III	*p*
Aldosterone antagonist				
Spironolactone	2	93	5	0.57
Finerenone	1	0	0	0.58
Loop and thiazide diuretics				
Furosemide	44	98	62	0.54
Hydrochlorothiazide	13	16	7	0.56
Indapamide	6	0	0	0.56
Chlortalidone	2	0	0	0.53

of finerenone, 2 studies have explored the frequency of HPK in CKD grade 3-4 in both patients with kidney disease (FIDELIO) and in those with cardiovascular outcomes (FIGARO), the studies reported a frequency of 1.2% and 2.3%, respectively; 0.6% of patients had to be admitted to hospital and 1.2% suspended treatment. No patients died [13-15]. In this study, 37 patients were treated with finerenone, and 1 patient with CKD-5 not managed with dialysis (0.15%) had mild hyperkalemia. Our study showed that ACEi/ARAII were the most commonly prescribed drugs in all the groups. Diuretics were the most common in peritoneal dialysis and calcium antagonists in hemodialysis, indicating that their benefits outweigh any associated effects.

Hyperkalemia is usually underestimated in CKD, since it is asymptomatic and subclinical. Therefore, as affected patients are accustomed to maintaining chronically high levels of potassium, they are vulnerable [16]. Patients with heart failure and reduced ejection fraction are also vulnerable. A Spanish consensus on the use of ACEi/ARAII in patients with serum potassium 5 mEq/L found therapy to be associated with improved functioning, increased quality of life, reduced probability of cardiovascular death, and reduced frequency of hospitalization; treatment is clearly supported by the additional benefits of these drugs on reducing elevated urine albumin and the presence of resistant arterial hypertension. Therefore, patients should avoid potassium intake and drugs that impair glomerular filtration and use agents that favour elimination via faeces and urine [17,18]. Electrocardiographic changes reflect severe hyperkalemia and generally necessitate a choice between conservative management and initiation of dialysis. The report from the KDIGO Controversies Conference defines the severity of hyperkalemia based on the highest potassium value and electrocardiographic changes. In the present study, the authors found electrocardiographic alterations in 11% of patients. The changes consisted in a pointed T wave and prolongation of the QR interval. There was no correlation between the potassium values or between the study groups. These results are similar to those reported in the literature, and no patients had severe arrhythmia or died. Given the risk of fatal arrhythmia resulting from cardiac membrane instability, hyperkalemia is considered a medical emergency [19-21] (Figure 3). Despite therapy for HPK, increased values are associated with daily intake of potassium and hydration status. Therefore, nutritional support is essential in line with the patient's individual needs [2,22]. While the World Health Organization recommends intake of 90 to 120 mEq/d in the general population, this is not applicable for patients with CKD or patients in dialysis; information provided by the physician and nutritionist should be precise, with emphasis on tailored regimens, since the fear of developing hyperkalemia resulting from diet often leads to failure to ingest the necessary nutrients. It is estimated that between 50% and 60% of potassium from fruit and vegetables and 80% of animal foods is absorbed in the intestine. Almost 100% of potassium additives in processed and highly processed foods are absorbed; therefore, a fibre-rich diet is essential [23,24]. Current drugs have proven useful for treatment of HPK, with clear evidence for patients receiving and not receiving dialysis (zirconium cyclosilicate) and under both acute conditions and for long-term management. Consequently, it is not necessary to discontinue treatment based on ACEi/ARA/selective mineral corticoid receptor antagonists in patients with heart disease or impaired kidney function, where use is restricted [25-28]. Given that the frequency of hyperkalemia was high in our study, it is necessary to develop strategies that enable it to be identified quickly and not underestimate the potentially severe independent effects of electrocardiographic changes. Appropriate treatment must be administered.

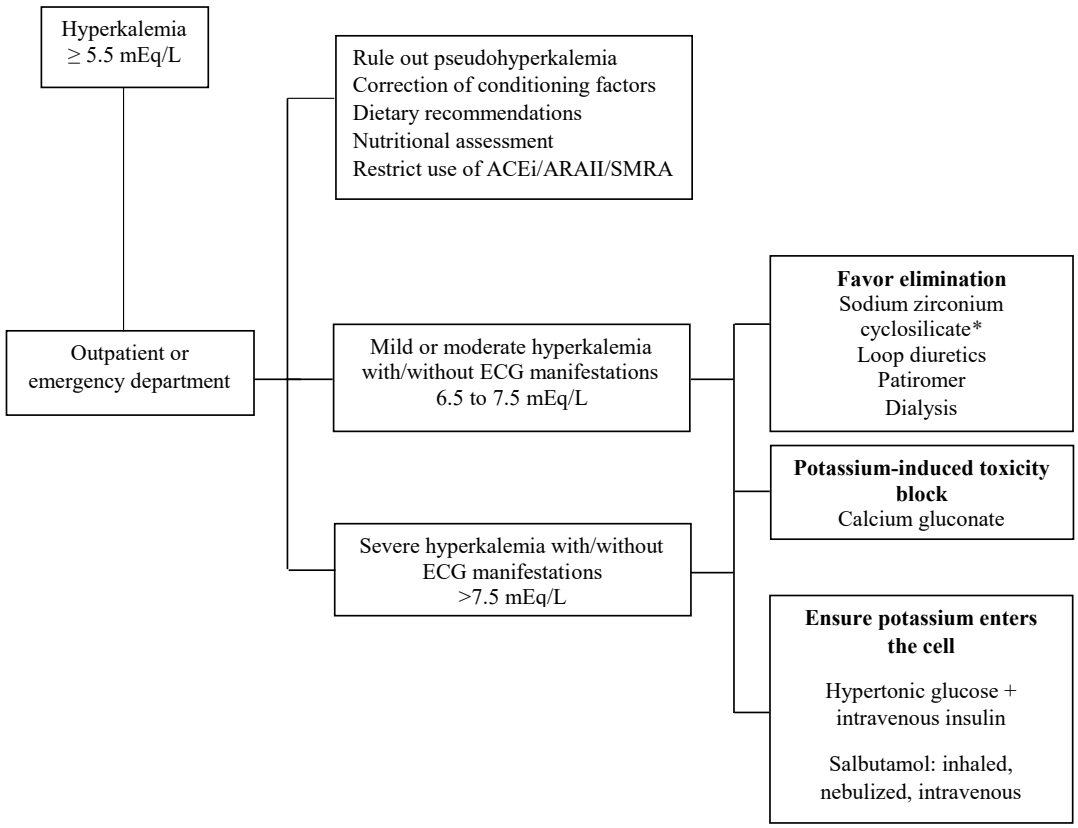

Figure 3: Management of hyperkalemia in renal failure managed with/without dialysis.
ACEi: Angiotensin-converting enzyme inhibitor; ARA: Angiotensin II receptor antagonist; SMRA: Selective mineralocorticoid receptor antagonist.

Conclusions

The frequency of hyperkalemia was high compared to other reports. The potential effects of the condition should not be underestimated, independently of electrocardiographic changes.

Contributions

Dr Antonio Méndez Durán designed the protocol and analyzed the data.

Drs Juan Daniel Díaz García, Ivonne Reyes Sánchez, Diana Carolina Sánchez Guerrero, Ramón Ruíz Mejía, Carlos Alberto Bello Soto, José Horacio Cano Cervantes, Socorro Méndez Balcázar, Francisco Fabián Rodríguez, and Luz Elena Vázquez Martínez collected data, reviewed the manuscript for publication († Equal contributor).

The nutritionists Imelda López Pérez and Alejandra Rivas Vera participated in the drafting and discussion of the manuscript, these authors share last authorship.

Acknowledgments

The authors thank Content Ed Net, Madrid, and Spain for editorial assistance.

Statement of Ethics

Data confidentiality was maintained at all times. Participating physicians were authorized to record data in their respective units.

Conflict of Interest

Emerson Joachín Sánchez and Gabriel Yáñez Boy are employees of AstraZeneca. The rest of authors declare that they have no conflicts of interest.

Funding

Given its nature, the study did not require biochemical material or equipment; the only expense was for stationery. The study generated no economic or care burden for the participating hospital unit. The investigators were volunteers and received no payment. Drafting of the manuscript and publication costs were supported by funds for education and research from AstraZeneca-México.

Data Availability Statement

All the data generated or analyzed during this study are included in the article. Requests for further information should be sent to the corresponding author.

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