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Cardiovascular Sequelae of Hypokalemia in Hemodialysis Patients

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Abstract

Background: Dyskalemia is a serious condition that encountered in End-Stage Renal Disease (ESRD) patients maintained on hemodialysis that may affect their prognosis. We aimed to investigate consequences of dyskalemia in such patients.

Patients and methods: Two-hundred hemodialysis patients underwent laboratory assessment of hemoglobin, blood sugar, renal function, serum albumin, parathormone, ferritin, ionized-calcium and phosphorus. Serum potassium was estimated before and within 2 hour after dialysis. Electrocardiogram (ECG) was obtained just before dialysis session. Transthoracic echocardiography was obtained within 2 hour after dialysis; estimating ventricular systolic and diastolic functions and pulmonary pressure. Twelve-month followed-up was undertaken for mortality.

Results: Patients were divided according to pre-dialysis potassium into hypokalemic (n=26), hyperkalemic (n=56) and normokalemic groups (n=118). Hypokalemic group were older with longer dialysis duration (p<0.001). Dietary potassium varied significantly among groups, with more concomitant medications used in hyperkalemic group (p<0.001). Hypokalemic group showed higher Blood Pressure (BP) (p=0.002), while hyperkalemic group showed lower heart rate (p=0.012). Lower serum albumin and calcium, higher urea, creatinine, phosphorus and parathormone levels were in hyperkalemic group (p<0.001). Hypokalemic group showed evident ECG changes (p=0.024), increased Left Ventricle (LV) mass (p=0.032) and diastolic dysfunction (P<0.001). Although tendency toward higher mortality in hypo and hyperkalemic groups, no significant difference was observed (p=0.19). Pre-dialysis potassium was negatively correlated with dialysis duration (p<0.001), diastolic BP (p=0.042) and LV mass (p=0.018), and positively correlated with hemoglobin level (p=0.017), serum albumin, phosphorus and parathormone (p<0.001).

Conclusion: Hypokalemia is as serious as hyperkalemia, being associated with significant cardiovascular consequences in patients on maintenance hemodialysis.

Keywords: Hypokalemia; Hyperkalemia; Hemodialysis; Left ventricular mass; Diastolic dysfunction

Introduction

Kidneys play a pivotal role in maintaining potassium homeostasis by excreting nearly 90% of excess potassium. The total body potassium approximates 50 mmol/kg, which is mainly intracellular with only 2% extracellular. The dietary potassium absorbed by intestine stimulates insulin release that facilitates intracellular potassium transport *via* membrane-NA/K-ATPase. As potassium excretion is a relatively slow process especially in those with end stage renal disease (ESRD), so without rapid trans cellular shift process hyperkalemic milieu will result. Poor dietary compliance, inadequate dialysis and concomitant polymedication may also aggravate dyskalemia in those patients [1-4]. Hyperkalemia have been looked for as a potential life threatening silent killer, being responsible for about 3.1 mortality/1000 patient, which was related mainly to disturbance in cardiac rhythm [5]. Because of its low prevalence; hypokalemia have gained less attention in hemodialysis patients. Nevertheless; it was related to increased incidence of ventricular arrhythmias especially in those with underlying cardiac disease [6]. The current study was to investigate the clinical, laboratory, cardiovascular and mortality sequelae of potassium disturbance in maintenance hemodialysis patients.

Patient and Methods

A prospective study that included 200 patients with ESRD maintained on regular hemodialysis at Minia University hospital dialysis unit, within the period from August 2016 to December 2017. Inclusion criteria: ESRD patients maintained on regular hemodialysis for more than 6 months using bicarbonate dialysate and low reflux membrane. Exclusion criteria: conditions that may affect potassium homeostasis as decompensated liver disease, corticosteroid administration, history of repeated vomiting and/or chronic diarrhea. All patients underwent thorough history taking including current symptoms, comorbidities, medications and their dietary potassium (The balanced-dietary potassium is 3500-4500 mg/day, potassium intake >4500 mg/day is considered as high-dietary potassium, while that less than 2000 mg/day is considered low- or restricted-dietary

potassium). Clinical examination was undertaken including estimation of Body Mass Index (BMI) and local cardiac examination. Laboratory investigations were obtained including Random Blood Sugar (RBS), hemoglobin, blood urea, serum creatinine, serum albumin, parathyroid hormone (parathormone), serum ferritin, serum ionized calcium (ca^{2+}) and phosphorus levels. Serum potassium (K+) level was estimated twice just before and within 2 hours after dialysis session, using AVL-9180 Analyzer methodology [7]. Twelve-lead resting electrocardiogram (ECG) was obtained from all patients just before the dialysis session. Resting Transthoracic Echocardiography study (TTE) was performed for all patients within 2 hours after the dialysis session, including estimation of left ventricle (LV) dimensions, Ejection Fraction (EF), wall thickness and LV mass using Devereux's formula, Right Ventricle (RV) systolic function by Tricuspid Annular Plane Systolic Excursion (TAPSE), mitral and tricuspid Doppler inflow pattern and annular tissue Doppler imaging for evaluation of LV and RV diastolic function, and Peak Systolic Pulmonary Artery Pressure (PSPAP) using tricuspid regurgitation peak velocity. Echocardiographic data was interpreted according to the recommendations for cardiac chamber quantification by echocardiography in Adults [8], by two echocardiographers independently. Patients were followed-up for 12 month for occurrence of mortality. Patients were classified according to their pre-dialysis potassium level into 3 groups; group I which included patients with hypokalemia (serum K+<3.5 mEq/l), group II which included patients with hyperkalemia (serum K+>5.5 mEq/l), and group III which included those with normal potassium level (serum K+=3.5-5.5 mEq/l). Statistical analysis: was performed using Statistical Package for the Social Sciences (SPSS) software, version 16.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Categorical and quantitative variables were respectively described as number/percentage (%) and mean ± SD. Non-parametric variables were compared by chi-square test, and Analysis of Variance test (ANOVA or F test) was used for comparison of more than two means. Correlation between variables was calculated by Spearman rho correlation coefficient. Statistical significance was defined as a probability level of $p<0.05$.

			Group I (Hypokalemic) n=26	Group II (Hyperkalemic) n=56	Group III (Normokalemic) n=118	P value
Age (years)		Range Mean ± SD	(35-69) 54.69 ± 10.85	(19-60) 41.78 ± 10.85	(19-65) 38.15 ± 11.38	<0.001
Gender	**Male**	no'(%)	16 (61.5%)	38 (67.9%)	68 (57.6%)	0.658
	Female	no'(%)	10 (38.5%)	18 (32.1%)	50 (42.4%)	
Duration on dialysis (years)		Range Mean ± SD	(3-15) 8.07 ± 3.92	(1-8) 3.76 ± 2.35	(1-14) 5 ± 3.11	<0.001
BMI		Range Mean ± SD	(16.6-24) 18.23 ± 2.03	(16-27) 20.21 ± 3.16	(17-29) 21.61 ± 3.36	0.002
Dietary potassium	**High**	no'(%)	4 (15.4%)	36 (64.3%)	6 (5.1%)	<0.001
	Low	no'(%)	20 (76.9%)	4 (7.1%)	4 (3.4%)	
	Balanced	no'(%)	2 (7.7%)	16 (28.6%)	108 (91.5%)	
Patients on chronic drugs		no'(%)	4 (15.4%)	42 (75%)	8 (6.8%)	<0.001
Patients with concomitant diseases	**HTN**	no'(%)	16 (61.5%)	30 (53.6%)	56 (45.8%)	0.533
	DM	no'(%)	4 (15.4%)	16 (28.6%)	16 (13.6%)	0.227
	CVD	no'(%)	2 (7.7%)	6 (10.7%)	4 (3.4%)	0.39
	HCV	no'(%)	4 (15.4%)	18 (32.1%)	26 (22%)	0.433
SBP (mmHg)		Range Mean ± SD	(110-160) 131.92 ± 17.14	(90-150) 122.85 ± 15.36	(90-150) 115.59 ± 15.62	0.002
DBP (mmHg)		Range Mean ± SD	(70-110) 86.92 ± 13.15	(65-95) 78.39 ± 7.82	(60-100) 75.08 ± 11.27	0.002
HR (beat/min)		Range Mean ± SD	(59-81) 69.46 ± 5.9	(49-70) 56.67 ± 8.5	(61-90) 75.06 ± 7.8	0.012

Table 1: Demographic and Clinical Data among Groups. BMI: Body Mass Index; HTN: Hypertension; DM: Diabetes mellitus; CVD: Cardiovascular Disease; HCV: Hepatitis C Virus; SBP: Systolic Blood Pressure; DPB: Diastolic Blood Pressure; HR: Heart Rate.

Results

The included 200 hemodialysis patients were classified according to their pre-dialysis potassium level into 3 groups; group I that included 26 hypokalemic patients, group II that included 56 hyperkalemic patients, and group III that included 118 normokalemic patients. No statistical difference was observed among groups regarding male/female percent and history of concomitant diseases (diabetes mellitus, hypertension, cardiovascular diseases, and viral hepatitis C).

The hypokalemic group were relatively older (p<0.001), with longer duration on dialysis (p<0.001) and with relatively lower BMI (p=0.002), while hyperkalemic group showed a significantly larger percent of those using concomitant medications (mainly angiotensin converting-enzyme inhibitors, angiotensin-receptor blockers, beta-blockers and non-steroidal anti-inflammatory drugs) (p<0.001).

A significant difference was observed regarding dietary potassium intake among the 3 groups (p<0.001).The hypokalemic group showed relatively higher systolic and diastolic blood pressure (BP) than the other groups (p=0.002), while hyperkalemic group showed relatively lower heart rate (p=0.012) (Table 1).

No statistical difference among the 3 groups regarding hemoglobin, random blood sugar and serum ferritin levels, while relatively lower serum albumin and Ca^{2+} level and higher serum phosphorus and parathormone levels were observed in hyperkalemic group compared to the other groups (p<0.001 for all). Moreover; relatively higher blood urea and serum creatinine levels were observed in the same group (p=0.014, p<0.001 respectively) (Table 2).

After dialysis session and according to post-dialysis serum potassium level; 79% of patients became normokalemic and 17% of patients became hypokalemic, while only 4% of patients remained hyperkalemic.

		Group I (Hypokalemic) n=26	Group II (Hyperkalemic) n=56	Group III (Normokalemic) n=118	P value
Hb (g/dl)	Range Mean ± SD	(6.9-12) 9.51 ± 1.66	(6.5-14) 10.58 ± 1.83	(5.3-14) 9.96 ± 1.35	0.08
RBS (mg/dl)	Range Mean ± SD	(121-190) 151.38 ± 23.76	(106-240) 157.82 ± 40.36	(123-236) 155.23 ± 27.92	0.828
Ferritin (ng/ml)	Range Mean ± SD	(113-2211) 1134.46 ± 614.17	(55-5210) 1481.75 ± 1217.89	(100-5220) 1268.88 ± 874.81	0.931
Ca2+ (mmol/l)	Range Mean ± SD	(1.8-5) 3.02 ± 1.11	(1.5-5) 2.73 ± 0.83	(2.3-6.1) 4.02 ± 0.92	<0.001
Phosphorous (mmol/l)	Range Mean ± SD	(2.5-6.1) 3.46 ± 1.02	(3.8-8.5) 6.34 ± 21.53	(3.6-6.3) 5.01 ± 0.79	<0.001
Parathormone (pg/ml)	Range Mean ± SD	(100-340) 209.65 ± 79.25	(213-2018) 662.73 ± 422.18	(153-1123) 257.57 ± 147.27	<0.001
Albumin (g/dl)	Range Mean ± SD	(2.3-4) 2.96 ± 0.47	(3.5-5.3) 4.26 ± 0.6	(3.2-5) 4.03 ± 0.49	<0.001
Urea (mg/dl)	Range Mean ± SD	(95-157) 121.07 ± 17.69	(99-167) 136.71 ± 17.53	(105-156) 134.77 ± 12.97	0.014
Creatinine (mg/dl)	Range Mean ± SD	(5.1-8.2) 6.43 ± 0.99	(4.4-11) 7.22 ± 1.76	(3.8-7.3) 5.81 ± 0.73	<0.001

Table 2: Laboratory Investigation results at different groups. Hb: Hemoglobin; Ca^{2+}: Calcium; RBS: Random Blood Sugar.

Regarding resting ECG; a significant difference was observed among groups (p=0.024), with more ECG changes in hypo and hyperkalemic groups compared to normokalemic group (Table 3). ECG changes in hypokalemic group were mainly LV Hypertrophy (LVH) (4 cases), T-wave inversion (4 cases), frequent ventricular extrasystoles (2 cases) and prominent U-wave (2 cases) while ECG changes in hyperkalemic group were mainly sinus bradycardia (12 cases), ST segment depression (6 cases), tented T-wave (4 cases), short QT-interval (2 cases), LVH (2 cases), and atrial fibrillation (1 case).

In normokalemic group; ECG changes were LVH (5 cases), ST-T changes (4 cases), frequent extrasystoles (1 case), atrial fibrillation (1 case), and left bundle branch block (1 case). Of note; more than one ECG changes were found in some patients.

Regarding resting TTE; no significant difference was observed regarding LV dimensions and EF%, TAPSE, RV diastolic function and PSPAP among groups, while significantly larger LV mass and higher incidence of LV diastolic dysfunction was observed in hypokalemic group compared to the other groups (p=0.032, P<0.001 respectively) (Table 3).

			Group I (Hypokalemic) n=26	Group II (Hyperkalemic) n=56	Group III (Normokalemic) n=118	P value
ECG changes		(%)	30.8%	28.6%	8.5%	0.024
LVIDd (mm)		Mean ± SD	50 ± 5.4	52 ± 4.6	47 ± 5.8	0.19
LVIDs (mm)		Mean ± SD	28 ± 7.1	34 ± 4.2	30 ± 3.8	0.082
LV mass (g)		Mean ± SD	254 ± 84	198 ± 65	210 ± 44	0.032
LV EF%		Mean ± SD	56.15 ± 7.4	57.39 ± 8.51	57.42 ± 8.01	0.872
LV DD	**Grade I**	no'(%)	12 (46.15%)	14 (25%)	22 (18.6%)	<0.001
	Grade II	no'(%)	12 (46.15%)	17 (30.4%)	34 (28.8%)	
TAPSE (mm)		Mean ± SD	24 ± 2.6	21 ± 3.9	22 ± 1.8	0.34
RV DD	**Grade I**	no'(%)	4 (15.4%)	11 (19.6%)	20 (16.9%)	0.443
	Grade II	no'(%)	2 (7.7%)	6 (10.7%)	12 (10.1%)	
PSPAP (mmHg)		Mean ± SD	46 ± 8.3	37 ± 12.7	41 ± 10.1	0.142
PHT:	**Mild**	no'(%)	6 (23.1%)	14 (25%)	20 (16.95%)	0.569
	Moderate	no'(%)	0	4 (7.1%)	20 (16.95%)	
	Severe	no'(%)	2 (7.7%)	2 (3.6%)	8 (6.8%)	

Table 3: ECG and Echocardiographic Data at different groups. ECG: Electrocardiogram; LV: Left Ventricle; LVIDd: LV Internal Diastolic dimensions; LVIDs: LV Internal systolic Dimensions; EF: Ejection Fraction; DD: Diastolic Dysfunction; TAPSE: Tricuspid Annular Plane Systolic Excursion; RV: Right Ventricle; PSPAP: Peak Systolic Pulmonary Artery Pressure; PHT: Pulmonary Hypertension.

In the 12-month follow-up; no statistically significant difference was observed in mortality among groups, nevertheless a tendency toward higher mortality in hypo and hyperkalemic groups (6 (23%), 8 (14%) and 4 (7%) in group I, group II and group III respectively, p=0.19).

Interestingly; 50% of mortalities were cardiovascular-related in both hypo and hyperkalemic groups (3 cases in hypokalemia group; 2 cases were due to heart failure and one case was due to pulseless ventricular arrhythmia, and 4 cases in hyperkalemic group; 3 cases were due to marked bradycardia and one case was due to cardiogenic shock), while only one mortality was due to cardiogenic shock in normokalemic group.

A significant negative correlation was observed between pre-dialysis serum potassium level with duration of dialysis, diastolic BP and LV mass (r=-0.371, r=-0.204, r=-0.376 respectively), and a significant positive correlation was observed with hemoglobin (r=0.238), serum albumin, phosphorus and parathormone levels (r=0.542, r=0.621, r=0.466 respectively). Meanwhile; no statistically significant correlation was observed between pre-dialysis potassium level with mortality or other echocardiographic parameters (Table 4).

Discussion

According to the pre-dialysis potassium level in the included 200 hemodialysis patients; 28% were hyperkalemic while 13% of patients were hypokalemic. Although this was discordant to previous studies that estimated the prevalence of hyperkalemia in maintenance hemodialysis patients by about 8.7-10% while hypokalemia was 0.3-0.5% [9,10], but Hwang et al. [11] stated that the precise prevalence of hypokalemia in hemodialysis patients is unknown and varies among different centers.

The duration on maintenance dialysis was negatively correlated with pre-dialysis potassium level, with a relatively longer duration in those with hypokalemia in our study. This may be explained by overcorrection of potassium disturbance by long-term maintenance on hemodialysis and following suitable diet regimens [12]. Similar relation between dietary potassium and pre-dialysis potassium level as expressed by our study had been reported by several previous studies [10,13]. Although similar results to ours regarding higher incidence of concomitant drugs intake in hyperkalemic patients were reported by Choi et al. [10] but the relation between potassium level and concomitant drug intake was insignificant in another study by El-Sharkawy et al. [4].

In the current study hypokalemic patients were relatively older, had lower BMI, blood urea and serum albumin. This was consistent with the results of Hwang et al. [11] who clued low BMI, blood urea and hypoalbuminemia in such patients to malnutrition.

In agreement to our results of higher BP in hypokalemic patients with negative correlation between pre-dialysis potassium and diastolic BP; Macdonald and Struthers [14] showed similar correlation, and explained it by lack of potassium-mediated vasodilation *via* strong inward rectifying potassium channels and Na/K-ATPase pump of vascular smooth muscle cells in such patients [12].

Our results showed that hyperkalemic patients had lower Ca^{2+}, higher phosphorus and parathormone levels, with positive correlation between pre-dialysis potassium and both phosphorus and parathormone levels. This was concordant to previous data by Ahmed

and Weisberg [15], who stated that parathormone may impair extra-renal disposal of potassium in ESRD, as it facilitates entry of calcium into cells with the rise in cytosolic calcium, which affects cellular permeability to potassium. de-Francisco et al. [16] clued such increase in parathormone level to the increase of serum phosphorus during hemodialysis that prevented inhibition of parathyroid by calcium. They also observed a concomitant reduction in the level of parathormone by decreasing serum phosphorus.

	Pre-dialysis serum potassium	
	r	P
Age	-0.216	0.031
Duration of dialysis	-0.371	<0.001
BMI	0.034	0.689
SBP	-0.111	0.273
DBP	-0.204	0.042
HR	-0.002	0.956
Hb	0.238	0.017
Ionized calcium	-0.089	0.19
Phosphorus	0.621	<0.001
Parathormone	0.466	<0.001
Albumin	0.542	<0.001
LV mass	-0.376	0.018
LV EF%	0.029	0.774
PSPAP	-0.167	0.095
LV diastolic function	0.108	0.283
Mortality	-0.017	0.87

Table 4: Correlation of Pre-dialysis Potassium Level with Different Demographic, Clinical and Echocardiographic Parameters, and mortality. BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; Hb: Hemoglobin; LV: Left Ventricle; EF%: Ejection Fraction Percent; PSPAP: Peak Systolic Pulmonary Artery Pressure.

The Hemoglobin level was positively correlated with pre-dialysis potassium level in our study. This may be explained by observation of Goodnough et al. [17] that impaired potassium homeostasis in uremia might be secondary to decrease Na/K-ATPase activity in skeletal muscles and other tissues, which was also associated with low level of erythropoietin and subsequently anemia. Moreover; being older and of low BMI, hypokalemic patients may have a reduced muscle strength with poor physical performance and disability [18].

Although the current study expressed more evident ECG changes in both hypo and hyperkalemic patients than normokalemic patients, only 28% of hyperkalemic patients who showed consistent ECG changes. Concordant to our results, previous studies had reported an increased incidence of ventricular arrhythmias from 9 to 40% with dyskalemia [6]. Also it was stated that hemodialysis patients may not exhibit the usual ECG sequence of hyperkalemia, possibly due to fluctuations in serum calcium concentration, concluding that absence of ECG changes in hyperkalemic should be interpreted with caution [14,19]. Moreover; we found a relatively lower heart rate in hyperkalemic patients and 21% of cases showed bradycardia. This was consistent with previous studies which reported a causal relation between hyperkalemia and bradycardia in ESRD patients [20].

A significant negative correlation was observed between pre-dialysis potassium level and LV mass, with significantly larger LV mass in hypokalemic patient in the current study. Similar results but in primary hyperaldosteronism patients were also observed by Lin et al. [21] concluding that low serum potassium was significantly associated with increased LV mass. In agreement to our results regarding the evident incidence of diastolic dysfunction in hypokalemic patients; Macdonald and Struthers [14] showed that potassium depletion produces diastolic dysfunction in animal and human models.

No significant relation was observed between pre-dialysis potassium level and mortality, with no statistically significant mortality difference among groups at 12 month follow-up in our study. Nevertheless; a tendency toward higher mortality was evident in hypo and hyperkalemic group, with 50% of mortalities were cardiovascular-related. Similar results were conducted by lee et al. in Korean ESRD patients maintained on dialysis followed-up for about 4 years. Although low pre-dialysis potassium represented an independent predictor of survival in overall dialysis especially in peritoneal dialysis patients, and U-shaped survival pattern was observed in hemodialysis patients, suggesting that both lower and higher potassium levels carried a deleterious prognosis in hemodialysis patient [22]. Moreover; Kovesdy et al. [23] showed that normal pre-dialysis potassium had been associated with the greatest survival in maintenance hemodialysis patients.

From the previously mentioned data; pre-dialysis dyskalemia was associated with significant cardiovascular changes in maintenance hemodialysis patients. It was associated with a higher incidence of ECG changes, but this may not be evident in all patients especially those with hyperkalemia. Hypokalemia was associated with higher BP especially the diastolic readings, evident echocardiographic changes in form of increased LV mass and relatively higher incidence of diastolic dysfunction. Further studies are needed to investigate its possible relation to more cardiovascular affection. Hyperkalemia was also associated with other electrolytes and hormonal disturbances which might affect their prognosis. Although pre-dialysis serum potassium level failed to express a statistically significant relation to the 12 months survival in hemodialysis patients; but a tendency towards higher cardiovascular mortality in those with pre-dialysis dyskalemia than those with normal potassium level. Further investigations on a larger scale of patients with a longer follow-up duration may be needed to confirm such relation.

Conclusion

Hypokalemia is as serious as hyperkalemia in patients maintained on regular hemodialysis, being associated with significant cardiovascular consequences as higher BP readings, evident ECG changes, increased LV mass and higher incidence of diastolic dysfunction, which might increase the risk of cardiovascular mortality, is such patients.

Compliance with Ethical Standards

The study protocol was approved by the 'Institutional Ethical Committee/Reviewing Board of Minia University Faculty of Medicine' and was in accordance with the 'World Medical Association Declaration of Helsinki' and subsequent amendments. Informed consent was obtained from all participants.

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