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NEPHROLOGY - ORIGINAL PAPER

Community-acquired hypokalemia in elderly patients: related factors and clinical outcomes

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Abstract
Purpose Electrolyte imbalance is a common problem affecting the elderly. Increased number of comorbidities and frequent use of drugs may contribute to increased risk of hypokalemia in the elderly. This study was performed to investigate the prevalence of community-acquired hypokalemia (CAH), risk factors for its development, related factors with hypokalemia, and morbidities and all-cause mortality rates (MR) of CAH in the elderly patients.
Methods Total of 36,361 patients aged above 65 years were screened retrospectively. Group 1 consisted of 269 elderly patients with potassium level ≤3.5 mmol/L, and group 2 (control group) consisted of 182 subjects with potassium level between 3.6 and 5.5 mmol/L. Etiologic factors of CAH, presence of comorbidities, duration of hospital stay, hospital cost, and clinical outcomes were recorded.
Results Prevalence of hypokalemia was found 3.24% in patients aged above 65 years. Duration of hospital stay, presence of ≥2 comorbid diseases, hospital cost, and MR were significantly higher in group 1 compared to group 2 (p < 0.001 for all). Loop diuretics, hydrochlorothiazides, beta agonists, inadequate oral intake, and female gender were all independent risk factors for CAH in elderly patients. Patients with ≥2 comorbid diseases were found to have greater risk of hypokalemia than the patients with <2 comorbidities.
Conclusions Length of hospital stay, hospital cost, and MR were higher in elderly with CAH. Female gender, hydrochlorothiazides, loop diuretics, and ≥2 comorbid diseases are the leading risk factors associated with CAH in elderly.

Keywords Hypokalemia · Elderly · Hospital cost · Prevalence · Gender

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Background

Elderly population is growing rapidly and it was estimated to reach 835 million in the year 2025 [1]. In Europe, it is estimated that this will be the 1/5 of the whole population. Increase in the average life expectancy may lead to more frequent problems in the elderly, which may contribute to the increase in hospital expenses [1].

Electrolyte imbalance is a common problem affecting the elderly. Total body potassium in elderly is reduced in comparison with young people (approximately 2500 vs 3000 mmol) [2]. Skeletal muscle contains as much as 75% of body potassium; therefore, loss of muscle mass with age may lower the total body potassium amount [3]. In addition, increased number of comorbidities and frequent use of drugs that may cause hypokalemia, may also contribute to increased risk of hypokalemia in the elderly [4].

Hypokalemia developed in the hospital prolongs hospital stay and leads to an increase in mortality [3]. There are several studies on the causes of hypokalemia developed in hospital in elderly patients [5]. Hypokalemia is prevalent in hospitalized patients, and its prevalence was reported to be between 6.7 and 20% in different trials probably due to different cut-off points and patient characteristics [6, 7]. However, there is lack of available data about community-acquired hypokalemia (CAH) in elderly patients.

This study was performed to investigate the prevalence of CAH, risk factors for its development, related factors with hypokalemia, and morbidities and all-cause mortality rates (MR) with CAH in the elderly patients.

Patients and methods

This study was approved by Human Research Ethics Committee (28.04.2016, 2016/135), and written informed consent was obtained from patients participating in the study.

Patients aged above 65 years, who were admitted to our hospital between May 2015 and April 2016, were evaluated for the presence of hypokalemia retrospectively. Hypokalemia was accepted as serum potassium levels ≤3.5 mmol/L [8]. The patients with serum potassium levels ≤3.5 mmol/L were evaluated in Group 1. Group 2 consisted of normopotassemic patients who had serum potassium levels between 3.6 and 5.5 mmol/L and served as control group.

Total of 36,361 patients aged above 65 years were evaluated. Prevalence of CAH was found as 3.24% (1180/36,361). Among 1180 patients with hypokalemia, group 1 consisted of 269 participants who met the inclusion criteria (119 male, 150 female). Of the patients with normal potassium levels, group 2 consisted of 182 patients who were randomly selected as control (109 male, 73 female).

Etiologic factors of CAH, presence of comorbidities, duration of hospital stay, hospital costs, and MR were recorded. Laboratory parameters as fasting plasma glucose, urea, serum creatinine, uric acid, albumin, sodium, potassium, bicarbonate, magnesium, calcium, high-sensitive C reactive protein [hCRP], free tyroxine [fT4], and thyroid-stimulating hormone [TSH] were tested in all patients. Arterial or venous blood gas analyses were also performed.

Arterial blood pressure was measured in all patients on admission (OMRON M6 Comfort, Kyoto, Japan). Serum sodium, plasma glucose, urea, and creatinine were measured by Olympus AU 640 Chemistry Immunoanalyzer (Tokyo, Japan). Serum potassium, magnesium, calcium, phosphor, albumin, TSH, fT4, and hCRP levels were measured by Cobas Integra 800 Chemistry Analyzer (Basel, Switzerland). Estimated glomerular filtration rate (eGFR) was calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula: 141 × min(Scr/κ,1) α × max(Scr/κ,1)−1.209 × 0.993 age × 1.018 [female] × 1.159 [black].

Exclusion criteria

Patients who developed hypokalemia during hospital stay, patients on chronic hemodialysis or peritoneal dialysis, patients with chronic myelocytic leukemia, chronic lymphocytic leukemia or essential thrombocytosis, pregnant women, patients with acute kidney injury, and renal tubular dysfunction or chronic kidney disease were all excluded from the study.

Comorbid diseases

Comorbid diseases were determined using ICD-10 (International Classification of Diseases, 10th revision). The presence of congestive heart failure (ICD-10: I50-51), hypertension (ICD-10: I10-11), diabetes mellitus (ICD-10: E11-14), chronic obstructive pulmonary disease (ICD-10: J44), Alzheimer's disease (ICD-10: F00), cerebrovascular disease (ICD-10: G45-46, ICD-10: I67-69), malignancies (ICD-10: C00-97), cirrhosis (ICD-10: K74), and Parkinson's disease (ICD 10: G20) were recorded. Association between the presence of two or more comorbid diseases and hypokalemia was investigated.

Etiology of hypokalemia

Use of loop diuretics, thiazides, gentamicine, ifosfamide, amphotericin B, cisplatin, insulin, beta agonists, theophylline, nasal decongestants (pseudoephedrine, ephedrine), vitamin B12, folic acid, chloroquine, antipsychotics (risperidone, quetiapin), and laxatives were recorded in both groups. The patients with primary hyperaldosteronism and other surrenal disorders, renal artery stenosis, vomiting, and diarrhea were also noted.

Treatment of hypokalemia

The patients who did not have severe hypokalemia had outpatient treatment consisted of oral potassium replacement (40–120 mEq), cessation of drugs which might cause hypokalemia and diet rich in potassium. These patients were checked after 1-week follow-up, and potassium treatment was stopped in patients, who had normal potassium levels. The patients who were unresponsive to -week oral potassium replacement therapy were hospitalized for further evaluation. However, on admission, the patients with insufficient oral intake or the patients who needed immediate replacement therapy (presence of the decreased T wave amplitude and U waves on electrocardiography, severe atrial and ventricular arrhythmias, and rhabdomyolysis) were hospitalized and intravenous route was preferred for replacement. Maximum 120 mEq potassium was given daily with maximum concentration of 40 mmol and infusion rate of 20 mmol/L.

Table 1 Laboratory and demographic data of the patients in both groups

	Group 1 ($n = 269$)	Group 2 ($n = 182$)	p value
Age, years	76.15 ± 6.8	75.19 ± 7.7	NS
Male	119	109	<0.05
Female	150	73	
Systolic blood pressure, mm Hg	142.5 ± 19.4	127.4 ± 6.5	<0.05
Diastolic blood pressure, mm Hg	84.9 ± 12.4	76.7 ± 4.6	<0.05
Pulse, minute	88.7 ± 16.1	82.1 ± 8.4	NS
Need for hospitalization, % (n)	49.8 (134)	36.3 (66)	<0.05
Length of hospital stay, days	4.2 ± 2.1	3.7 ± 2.1	<0.05
≥2 comorbid diseases, % (n)	75.8 (204)	17.4 (32)	<0.001
Potassium, mmol/L	3.1 ± 0.2	4.4 ± 0.5	<0.001
Fasting plasma glucose, mg/dL	135.7 ± 57.8	100.9 ± 33.8	<0.05
Urea, mg/dL	43.3 ± 32.5	39.0 ± 9.0	NS
Creatinine, mg/dL	0.73 ± 0.17	0.64 ± 0.2	NS
Sodium, mmol/L	136.4 ± 10.2	135.2 ± 10.6	NS
Albumin, g/dL	3.7 ± 0.3	3.6 ± 0.2	NS
Magnesium, mg/dL	1.8 ± 0.3	2.9 ± 1.7	<0.05
Calcium, mg/dL	8.7 ± 1.2	8.9 ± 1.3	NS
Hemoglobin, g/dL	12.1 ± 1.8	12.4 ± 1.9	NS
TSH, mikroIU/mL	1.9 ± 0.7	2.0 ± 0.6	NS
hCRP, mg/L	9.2 ± 11.8	9.6 ± 5.2	NS
pH	7.51 ± 0.03	7.37 ± 0.3	<0.05
Bicarbonate, mEq/L	31.03 ± 2.4	25.0 ± 2.1	<0.05
PO_2	91.9 ± 1.6	93.1 ± 1.7	NS
eGFR, mL/min/1.73 m^2	83.4 ± 10.6	96.01 ± 4.4	NS
Cost, USD$	616.3 ± 407.6	120.3 ± 91.1	<0.001
Mortality, % (n)	14.1 (38)	7.7 (14)	<0.001

TSH thyroid-stimulating hormone; *PO_2* oxygen pressure; *eGFR* estimated glomerular filtration rate; *USD$* United States dollars

Statistical analysis

MedCalc packet program was used for statistical analysis. Shapiro–Wilk test was used to identify whether variables were in normal distribution. Mean ± standard deviation was used for descriptive statistics. The mean comparisons of binary groups were made with Student's t test. Spearman correlation was used to test correlation between two continuous variables. Chi-square statistics was used to compare two categorical variables, and logistic regression analysis was used to evaluate the risk factors for hypokalemia in a multiple model.

Results

Baseline characteristics

Demographic and laboratory data of the patients in both groups are shown in Table 1. Serum potassium level on admission, duration of hospital stay, presence of ≥2 comorbid diseases, hospital costs, and MR were significantly higher in group 1 compared to group 2 ($p < 0.001$ for all).

In group 1, it was found that 142 (52.7%) patients used hydrochlorothiazides, 47 (17.4%) used loop diuretics, and 43 (15.9%) used beta agonists. Fifty-two (19.3%) patients in group 1 had a history of inadequate oral intake. In group 2, 12 (7.1%) patients had a history of hydrochlorothiazides use, 12 (6.5%) loop diuretics use, and 9 (4.9%) beta agonists use. Eight (4.3%) patients had inadequate oral intake in group 2. These differences were found to be statistically significant ($p < 0.05$).

Use of hydrochlorothiazides in group 1 was more frequent among elderly female patients than elderly males (56 vs 32.8%, $p < 0.05$). Eighty-six percent of the females and 44.5% of males had ≥2 comorbid diseases ($p < 0.05$). Need for hospitalization, hospital cost, and MR were significantly higher in females than in males ($p < 0.05$). There was no significant difference for the other etiologic agents between two genders ($p > 0.05$) (Table 2).

Table 2 Need for hospitalization, hospital cost, and clinical outcomes of patients in group 1

	Males	Females	*p* value
Need for hospitalization, % (*n*)	42 (50)	54.6 (82)	<0.05
Exitus, % (*n*)	10.1 (12)	17.3 (26)	<0.05
Cost, USD$	466.3 ± 213.2	735.3 ± 253.4	<0.05

USD$ United States dollars

Risk factors for hypokalemia

We found that age was not an independent risk factor for CAH (OR 1.019; 95% CI 0.992–1.046). Female gender was found to increase the risk of hypokalemia compared to males (OR 2.22, 95% CI 1.16–4.22). Patients with ≥2 comorbid diseases were found to have greater risk of hypokalemia than the patients with <2 comorbidities. Loop diuretics, hydrochlorothiazides, and beta agonists were all independent risk factors for CAH in elderly patients. In addition, inadequate oral intake was also independent risk factor for hypokalemia. Risk analysis of hypokalemia in all patients we evaluated is shown in Table 3.

Hypokalemia and related factors

In group 1 patients, there was negative correlation between serum potassium and age, systolic blood pressure (SBP), diastolic blood pressure (DBP), eGFR, number of the drugs used, number of the comorbidities, treatment period, duration of hospital stay, and hospital costs (for all $p < 0.001$, r values, respectively: $r = -0.471$, $r = -0.928$, $r = -0.681$, $r = -0.256$, $r = -0.360$, $r = -0.399$, $r = -0.488$, $r = -0.938$, $r = -0.826$).

Hypokalemia was shown to increase the risk of both systolic (OR 2.01, 95% CI 1.655–2.014) and diastolic hypertension (OR 1.93, 95% CI 1.542–1.982).

Table 4 Mean potassium values with respect to the gender, comorbid diseases, and clinical outcomes in group 1

		Potassium	
		Mean	*p* value
Gender	Male	3.263 ± 0.16	$p < 0.001$
	Female	3.012 ± 0.27	
Comorbidity	Comorbidities <2	3.261 ± 0.16	$p < 0.001$
	Comorbidities ≥2	3.080 ± 0.27	
Clinical outcome	Patients recovered	3.22 ± 0.33	$p < 0.001$
	Exitus	2.91 ± 0.41	

Clinical outcomes

Hospital cost was higher for patients in group 1 than those in group 2 (Table 1). Hospital cost was also found to be higher in female patients than in male patients in group 1 (Table 2).

Mean potassium values in group 1 with respect to sex, comorbidities, and clinical outcomes are shown in Table 4. Potassium level was lower in females compared to males, in patients with two or more comorbid diseases compared to patients with less than two comorbid disease, and was lower in patients who died compared to the patients who recovered.

Hypokalemia increased the risk of MR (OR 1.97, 95% CI for risk: 1.037–3.759; $p = 0.039$). Mean baseline potassium value was lower in patients who died than in those who recovered (2.9 ± 0.4 vs 3.2 ± 0.3 mmol/L, respectively) ($p < 0.05$).

Discussion

In the literature, there are many studies performed to find out the risk and related factors of hypokalemia in general population. However, the risk and related factors of CAH

Table 3 Logistic regression analysis for risk factors for hypokalemia

	β	SE	Wald	*df*	Sig.	OR (95% CI)
Female gender	0.79	0.32	5.932	1	0.011	2.22 (1.16–4.22
Loop diuretics	1.99	0.44	20.577	1	0.001	7.34 (3.10–17.38)
Thiazide diuretics	2.95	0.39	55.224	1	0.001	19.12 (8.78–41.64)
Inadequate oral intake	1.36	0.55	6.090	1	0.014	3.90 (1.32–11.53)
Comorbid diseases ≥2	3.66	0.37	98.141	1	0.001	39.13 (18.94–80.83)
Beta agonists	1.14	0.50	5.091	1	0.020	3.15 (1.16–8.56)

β logistic coefficient; *SE* standard error; *df* parameter coefficient, *OR* odds ratio; *CI* confidence interval in elderly people have not been studied yet. Therefore, to the best of our knowledge, this is the first study performed to find out the prevalence, risk factors, related comorbidities, and MR due to CAH in the elderly. Impact of female gender on the development and clinical outcomes of CAH is also demonstrated in this study.

It is not clear in the literature whether elderly females are more susceptible to hypokalemia than elderly males. Although plasma potassium level of elderly is in normal range, they are more susceptible to hypokalemia than younger individuals [7]. Sagild et al. [9] carried out a study by using radioactive isotope of potassium (K^{52}) in 1950 and found that the highest total potassium level was in males younger than 30 years (49.3 mmol/kg), whereas the lowest total potassium level was in females older than 60 years (27.9 mmol/kg). These results were independent from the cause of hypokalemia. The authors believed that the results might be associated with the lower body mass of women compared to men [9]. The presence of comorbidities and hydrochlorothiazide use was also more common in elderly females than in males in our study. So the question arises whether sex is the factor which makes the difference or if the difference is only related to the more common comorbidities and hydrochlorothiazide use in elderly females. The major reason for the marked decrease of potassium in females may be the reduced muscular mass. Loss of muscular mass by approximately 15% in the elderly, being more apparent in females, results in the reduced total body potassium which is mainly stored in the muscle. Female gender was previously documented as a predisposing factor for hypokalemia, and decreased prevalence of hypokalemia was seen in males [10]. Kleinfeld et al. [4] reported higher prevalence of hypokalemia developed in hospitalized females aged more than 65 years in comparison with males aged above 65 years and females aged below 65 years. Rodenburg et al. showed that the pharmacokinetics and pharmacodynamics were different in females and males in a study performed on 9.287.162 participants, and the authors suggested that females were more susceptible to drug adverse effects. In the same study, adverse effects of drugs was also found 1.5–1.7 times greater in females than in males and need for hospitalization due to drug adverse effects was more common in females than in males [11]. In our study, hypokalemia was more common in elderly females than in elderly males and female gender was an independent risk factor for hypokalemia. In addition, female elderly patients used hydrochlorothiazides more frequently than males. This might be the reason of the fact that hypokalemia is more common in females. In our study, hospitalization rate, MR, and hospitalization cost were higher in elderly females than in males. Lower potassium levels in elderly females may lead to higher MR and hospital cost.

In general population, inadequate oral intake, gastrointestinal and renal losses are the most common reasons for hypokalemia. Specific medications such as diuretics are one of the leading risk factors for hypokalemia. Diuretics except from potassium sparing ones may cause hypokalemia due to renal potassium excretion [6]. Thiazide-type diuretics may often be a part of an antihypertensive therapy, and hypokalemia development was reported in 13% of patients using thiazide-type diuretics [12]. Hydrochlorothiazides take an important place among the drugs causing hypokalemia in general population. In the same study, the patients who took hydrochlorothiazides had 11 times greater risk of hypokalemia [13]. Marti et al. reported hypokalemia prevalence as 13% in general population (mean age 56 years) in emergency department. They suggested that the most common reasons for hypokalemia were thiazide use and nausea-vomiting [14]. In our study, we investigated the etiology of CAH in a more specific population (patients aged >65). We found that the use of drugs, especially hydrochlorothiazides, is the most common reason of hypokalemia in elderly, which were consistent with results obtained in previous studies. More than half of the patients used hydrochlorothiazides, whereas 1/5 of them used loop diuretics.

We found that the risk of hypokalemia was higher in patients havingtwo or more comorbidities in the present study, but the exact underlying mechanism is unclear. The patients may be more prone to potassium loss in the presence of comorbidities [15]. In addition, increased number of comorbidities may lead to hypokalemia due to loss of appetite, decreased oral intake, and impaired absorption of potassium from gastrointestinal tract [16].

Hypokalemia is an electrolyte disorder associated with hypertension. There are different underlying mechanisms for this relation. Some of these patients had secondary hypertension such as primary hyperaldosteronism [17]. There were several studies demonstrating the direct effects of hypokalemia on the development of hypertension [18, 19]. Liamis et al. carried out a study about community-acquired electrolyte impairment in patients aged over 55 years and reported that hypokalemia was associated directly with hypertension. Risk of hypertension was found to be 2.73 times more in these patients [16]. Similar to this study, we found that both SBP and DBP on admission were inversely correlated with hypokalemia. Hypokalemia was also found as an independent risk factor for both systolic and diastolic hypertension in our study.

Hypokalemia leads to higher rates of hospitalization and longer length of hospital stay due to its cardiac and neuromuscular complications. This was demonstrated in a study performed by Scotto et al. in patients with hypokalemia (mean age 65.5 years) in intensive care unit. Mean hospital cost of patients who were hospitalized due to hypokalemia was reported as 231 United States Dollars (USD$) in this study [15]. In our study, need for hospitalization, length of hospital stay, and hospital cost was higher in the patients with hypokalemia compared to control group. Hypokalemia was correlated positively with the length of hospital stay and hospitalization rate in our study. Mean hospital cost of our patients was 616.3 ± 407.6 USD$. The hospital cost found in our study was higher than the cost found in the study by Scotto et al. The difference in the hospital cost between our study and the Scotto's study may be due to the fact that cost of health expenses may vary in different countries.

Low serum potassium level was associated with increased MR in different studies [20, 21]. Mild hypokalemia is a poor prognostic factor in elderly patients and even low-normal potassium levels were associated with higher mortality among community-acquired elderly people [21]. Liamis et al. [16] reported that hypokalemia could increase the risk of mortality 1.94 times in a study consisting of 5179 patients, aged >55 years. In our study, mean potassium value of the patients who died was 2.9 mmol/L, whereas it was 3.22 mmol/L for the patients who recovered. At the same time, hypokalemia was recognized as an independent risk factor for MR in our study.

One of the limitations of this study is the small sample size of patients and control groups to determine the risk and related factors of hypokalemia. Second limitation of the study is its retrospective design. Long-term prospective and larger sample size studies are required for more reliable results.

Conclusions

Prevalence, LHS, HC, and MR of CAH were higher in elderly. Female gender, hydrochlorothiazides, loop diuretics, and multiple comorbidities are the leading and independent risk factors associated with CAH in elderly people. Patients with multiple comorbidities and with inadequate oral intake should be followed more closely for CAH. If the concomitant use of the drugs which can cause hypokalemia such as hydrochlorothiazides, loop diuretics, and beta agonists is essential, clinicians should be more careful for the development of hypokalemia.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants 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 Informed consent was obtained from all individual participants included in the study.

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