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Beyond retrospective evidence: Role of Drugs, Diseases, and Drug–Disease Interactions in potassium abnormalities in older adults

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Abstract

Purpose

Potassium abnormalities in older adults are scantily studied in prospective designs. The contributors to potassium abnormalities are inadequately characterized across drug-related, disease-related, and drug-disease interaction-related domains.

Methods

Prevalence and risk factors for hypokalemia and hyperkalemia were explored in older adults in a tertiary hospital of North India from April 2023 to December 2024. Patients were categorized into group A (drugs were the primary cause of potassium abnormalities), group B (drugs were one among other causes), and group C (drugs were not the cause).

Results

Among 411 cases, hypokalemia was noticed in 56 (13.6%) patients. Drugs alone contributed to 64.3%, and diuretics were implicated in 46.4% of cases of hypokalemia. Levetiracetam, diuretics, and female sex were associated with 6.45 (1.19–34.66), 2.94 (1.6–5.4), and 1.83 (1.0-3.3) times higher adjusted odds of hypokalemia. Hyperkalemia occurred in 32 (7.8%) patients, and drugs in the setting of kidney disease were the commonest cause, followed by kidney disease alone. Hyperkalemia was associated with male sex and underlying kidney disease. Neither potassium abnormality was associated with increased mortality; however, a numerically higher mortality (20%) was observed in group C compared to group A (2.8%) for hypokalemia.

Conclusion

Every fifth hospitalized older adult has a potassium abnormality, and drugs are significant contributors. Favorable outcomes accompany prompt withdrawal of the culprit drug in hypokalemia, while a greater fraction of non-drug causes is associated with higher mortality. Sex-specific modulation of potassium abnormalities needs mechanistic insights, and newer associations, such as with levetiracetam, warrant larger studies involving diverse ethnicities.

1. Introduction

Potassium abnormalities are a common electrolyte disturbance in hospitalized patients. Undiagnosed, they are associated with higher mortality, particularly in patients with cardiovascular diseases.**[1]** Studies on the prevalence and etiology of potassium abnormalities in older adults are scarce in hospitalized settings, and the few existing studies are limited by retrospective designs.**[2, 3]** Prospective studies on

potassium abnormalities in older adults are predominantly scarce. Importantly, potassium abnormalities have not been studied discretely in the context of drugs, diseases, and drug-disease interactions. In the context of polypharmacy and drug-disease interactions, which are prevalent in older patients and the expanding availability of new drugs, the objective of the present study was to analyze the potassium abnormalities in older adults at the time of hospital admission with an emphasis on drug-related, disease-related, and drug-disease-related etiologies.

2. Methodology

Study Design: This is a subgroup analysis of a prospective study on dyselectrolytemia which was carried out in the inpatient department (IPD) of Geriatric Medicine in the Sir Sunder Lal Hospital in North India.

Study period: The study was initiated with the enrolment of its first patient in April 2023, and recruitment was completed by December 2024.

Study participants:

Inclusion criteria: In accordance with the hospital registration policies, patients who were ≥50 years of age were allowed admission in the study site. After the first few months, the age cut-off for hospital admission in the index unit was changed to 60 years. The data, hence, largely pertains to elderly patients aged 60 years and above.

Exclusion criteria: Patients for whom informed consent could not be obtained were excluded.

Definitions used:

Hypokalemia was defined as serum K^+ < 3.5 mEq/L and hyperkalemia as serum K^+ > 5 mEq/L. **[4, 5]** Severity of hypokalemia was rated as: mild (serum K 3-<3.5 mEq/L), moderate serum K (2.5-<3 mEq/L), and severe (serum K^+ < 2.5 mEq/L. **[6]** Hyperkalemia was categorized as mild (serum K^+: 5-5.9 mEq/L), moderate (serum K^+: 6-6.4 mEq/L), and severe (serum K^+ ≥ 6.5 mEq/L). **[5]** Based on the association of drug use with hyperkalemia or hypokalemia, patients were classified into three groups.

Group A: Patients in whom drugs were the leading or the sole cause of potassium abnormality

Group B: Patients in whom drugs contributed to potassium abnormalities along with other etiologies.

Group C: Patients in whom drugs were not involved, and other aetiologies were considered responsible for the potassium abnormality

Grouping of individuals was in accordance with the joint agreement of the interdepartmental team, composed of a geriatrician and a clinical pharmacologist specializing in geriatric drug therapy.

Ethical permission: The Institutional Ethics Committee approved the study before its commencement. Written informed consent was taken from patients or their respective caregivers.

Statistical analysis: Descriptive data were summarized as mean or median based on normalcy, and chi-square was used to look for the association of potassium abnormalities between drugs and medical factors. Variables with statistically significant associations (P < 0.05) were incorporated into the regression model, and binary logistic regression was utilized.

3. Results

3.1. Hypokalemia:

3.1.1. Prevalence and causes

Among 411 admissions (230 males) with a mean age (± SD) of 71.38 (±8.69) years, hypokalemia was present in 56 (13.6%). Demographics and other baseline features are mentioned in **Supplementary Table 1.** Drugs (group A) alone were responsible for the majority of cases (n=36, 64.3%), followed by non-drug causes in group C (11, 19.6%). Group B constituted two cases. Details are given in **Table 1**. Overall, more than one drug was involved in 13 cases (23.2%). Among drug classes, diuretics were implicated in 26 (46.4%) cases overall. Torsemide was the most common individual drug (n=10), followed by furosemide (n=8). The next common classes were antimicrobials and beta-agonists (n=7 each, 12.5%). Salbutamol nebulization was implicated in all seven cases where a beta agonist was suspected. Among antimicrobials, the commonest individual drug was levofloxacin (n=3) followed by injection amikacin and injectable linezolid (n=2, each). Xanthines such as theophylline were involved in three cases (5.3%). The frequency and % of common drug classes responsible for hypokalemia are displayed in **Figure 1.**

In group C, dehydration in the form of gastrointestinal loss was the commonest etiology for hypokalemia. Hypokalemia was associated with hyponatremia (serum Na^+< 135) in 31 (55.3%) cases.

3.1.2. Risk factors for hypokalemia:

Table 2 shows the unadjusted risk factors of hypokalemia. With statistical significance, a higher occurrence of hypokalemia was noticed in females and patients with malignancies. Among drugs, a positive association was observed with diuretics, levetiracetam, and ondansetron. (**Supplementary Table 2**) Hypokalemia shared a positive association with the number of drugs and some other drug classes, such as sulfonylureas and calcium channel blockers, but with a marginal statistical significance.

Factors with statistically significant association (P <0.05) with hypokalemia were analyzed using logistic regression for adjustment of confounders. (**Table 3**). With statistical significance, the adjusted odds (aOR) of hypokalemia were 6.45 (1.19-34.66), 2.94 (1.6-5.4), and 1.83 (1.0-3.3), respectively, with levetiracetam, diuretics, and female sex. With a marginal statistical significance (P=0.057), a 2.86 times higher aOR of hypokalemia was observed with underlying malignancies. No statistically significant association was noticed with ondansetron.

3.1.3. Severity and outcomes of hypokalemia:

Median (Q1-Q3) K^+ levels in group A and group C were 3.0 (2.9-3.2) and 2.9 (2.7-3.0) mEq/L. Mean K^+ levels in group B were 2.6 mEq/L. Category-wise, 5.5% and 18.2% of patients, respectively, in groups A and C, had severe hypokalemia.

Oral potassium supplements, intravenous KCl, and spironolactone were required in 45, 16, and 3 patients. Serum potassium improved fully in 46 (82.1%), and no improvement was noticed in three. Outcomes were not known for 5, and partial improvement was recorded in two.

Mortality rates were not different between patients with (5.5%) and without hypokalemia (5.2%). A numerically higher rate of mortality was visible in group C (20%) compared to group A (2.8%), however, with no statistical significance (P value: 0.22)

3.2. Hyperkalemia:

3.2.1. Prevalence and causes

Hyperkalemia was present in 32 patients at the time of admission, giving a point prevalence of 7.8%. Drugs in the setting of kidney disease (Group B) constituted the most common category. followed by kidney disease alone (Group C). Collectively, kidney disease as a cause was present in 26 cases (81.2%), and drugs contributed to hyperkalemia in 17 cases (53.1%). Among drugs, angiotensin receptor blockers (ARBs, n=8) and aldosterone antagonists (n=7) were the common classes implicated, and telmisartan and spironolactone were the commonly involved individual drugs. (**Table 4**) In unadjusted analysis, a positive association of hyperkalemia was observed with male sex, chronic kidney disease, and benign prostatic hyperplasia. (**Supplementary Table 3**) Within drugs, a positive association of hyperkalemia was noticed for diuretics, aldosterone antagonists, beta blockers, calcium channel blockers, statins, systemic anticholinergics, metformin, and dipeptidyl peptidase inhibitors (DPP-4). **(Supplementary Table 4**) However, because of the small number of events of hyperkalemia and, on the contrary, a large number of independent variables, we abandoned the plan of performing a regression for risk factors of hyperkalemia.

3.2.2. Severity and outcomes of hyperkalemia:

The median (Q1-Q3) values of serum K^+ were 5.8 (5.7-5.9 mEq/L), 5.4 (5.3-5.9), and 5.5 (5.3-5.7) for groups B and C, respectively. Nebulization with salbutamol was the most frequently employed treatment approach (21, 66%) for hyperkalemia. This was followed by injectable calcium gluconate (15, 47%). Oral potassium binders (calcium polystyrene sulfonate) and insulin infusion in 25% dextrose were required in 11 patients (34.4%). Serum K improved fully in 29 (90.6%). Hyperkalemia was not associated with high mortality (0% versus 5.7% in patients without hyperkalemia).

4. Discussion

We observed hypokalemia in around 14% of admissions, and drugs were the major cause in nearly 2/3rd of cases. More than one drug was involved in nearly a quarter. While diuretics were the most common class implicated, antimicrobials and beta agonists were involved in 12.5% each. The adjusted odds of hypokalemia were nearly 6.5, 3, and 2 times higher with levetiracetam, diuretics, and female sex, respectively. With marginal statistical significance, nearly 3 times higher odds of hypokalemia were observed with malignancies. Hypokalemia at the time of admission was not associated with in-hospital mortality

Previously, the prevalence of potassium abnormalities in hospitalised adults was shown to be close to 14%, and nearly 3.4-6.7% of adult patients can have hypokalemia at the time of hospitalisation. **[7, 8]**. The rates of hypokalemia in older adults, as noticed in the present study, are thus higher than the adult-specific estimates. A greater percentage of hypokalemia in hospitalised adults may be iatrogenic or hospital-acquired **[8]**. Hypokalemia is multifactorial in a greater percentage of cases, and gastrointestinal losses and diuretics have been common etiologies. **[7, 8].** In nearly a quarter of cases, hypokalemia co-existed with hyponatremia. **[8]** We observed hyponatremia in 55% of cases of hypokalemia.

Drugs have been implicated in 38% of cases of hypokalemia in adult-based studies, with diuretics, steroids, insulin, and vitamin B12 being the common culprit drugs. Diuretics were involved in 23.8%, and hypokalemia was associated with increased mortality and female sex. Disease-wise, patients with gastrointestinal and haematological malignancies were likely to suffer from hypokalemia. **[9].** The association of hypokalemia with mortality was refuted in the present study, but a marginally significant association was noticed with malignancies, which needs further confirmation.

Elderly specific prospective studies on hypokalemia are scarce. Studies are limited to community settings and are of retrospective designs **[3, 10].** Some older studies have shown a prevalence of hypokalemia close to 16% in older patients in hospitalized settings. **[11]** A higher vulnerability to hypokalemia in elderly females has been highlighted in all of them.

The significant association of hypokalemia observed with diuretics is expected. The high risk of hypokalemia in older females validates the findings of other epidemiologic studies limited to the elderly. Reasons for the increased vulnerability of elderly females to hypokalemia, however, remain obscure. The risk of hypokalemia with levetiracetam is perhaps a novel finding and warrants biological studies to understand the causality. Notwithstanding the high aOR, the confidence intervals for risk with hypokalemia were wide, and hence a cautious interpretation is suggested. Previously, in a retrospective comparative cohort based on electronic health records of Saudi Arabia, an increased hazard of hypokalemia 1.99 (95% confidence interval, 0.88–4.49) was witnessed in patients with exposure to levetiracetam. However, a higher percentage of levetiracetam users were on concomitant diuretics and insulin, the drugs classically linked with hypokalemia. **[12].** Other than this study, evidence surrounding levetiracetam and hypokalemia is limited to a few case reports. **[13, 14]**

Regarding hyperkalemia, close to 8% hospital admissions had elevated serum potassium levels. Drugs alone were a less common cause. Drugs in the setting of underlying kidney disease contributed to nearly

half of the cases of hyperkalemia. Previously, close to 3.3% rates of hyperkalemia have been reported in hospitalised patients, and a similar rate (2.94%) of hyperkalemia has been reported in elderly patients in retrospective designs. **[2, 15, 16]**Thus, the prevalence of hyperkalemia may be higher in prospectively designed studies. Similar to the present study, a many-fold increased risk of hyperkalemia was suggested with RAAS blockers and NSAIDs in older patients with underlying kidney disease. **[2]** The unadjusted association of hyperkalemia with BPH, and certain classes such as systemic anticholinergics, statins, metformin, calcium channel blockers, and DPP-IV inhibitors, might have been coincidental because of the small number of hyperkalemia events and hence were not taken for regression to prevent the generation of any overfitting model showing spurious risk associations.

5. Limitations

The study was conducted in a tertiary hospital in North India, and hence, findings cannot be extrapolated to other ethnicities. Serum magnesium and electrocardiogram were not available for all patients. Likewise, pH imbalances and acid-base disorders were not evaluated. Patients with hyperkalemia were few, and this prevented the authors from performing separate regression. Larger studies are required to understand the medical and drug-related determinants of hyperkalemia in older patients.

6. Conclusion

Around one in five older adults has a potassium abnormality at hospitalization, and medications are a significant contributor. The findings reinforce the importance of a clinical pharmacologist with expertise in geriatric drug therapy in guiding the therapeutic decisions for older patients. While a greater fraction of non-drug causes is associated with higher mortality, prompt withdrawal of the offending drug in hypokalemia is accompanied by favorable outcomes. Adequately powered studies are warranted to understand the unexplored drug-related risk factors of hyperkalemia. Sex related modulation of hypokalemia in older patients needs mechanistic insights, and emerging associations, such as with levetiracetam, warrant larger studies involving diverse ethnicities.

Declarations

Data availability statement: Due to privacy concerns, the data used in this manuscript can be made available on justified request to the corresponding author as per local and national laws and regulations.

Ethics Approval: The study was conducted with approval from the Institute Ethics Committee of the Institute of Medical Sciences, Banaras Hindu University, vide letter no. Dean/EC/2022/3157.

All procedures were performed as per the Declaration of Helsinki and its subsequent modifications.

Consent to Participate: Written informed consent was obtained from all patients (or legal guardians of patients) involved in the parent study. All procedures were performed as per the Declaration of Helsinki and its subsequent modifications.

Conflict of interest: None

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Authors' contributions: Upinder Kaur: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources, Writing- Review & Editing, Supervision, Project Administration

Abhimanyu Velmurugan, Aditi Pandey, Mahek Rai, Kshitij Kumar Prasad, Telagamsetti Sesha Sai Lahari, Tushar Varshney, Shaunak Majumdar: Validation, Investigation, Data Curation, methodology

Jyoti Agrahari and Shravani Bhattacharya: Validation, Formal Analysis, Investigation, Visualization

Anup Singh: Investigation, Project Administration

Sankha Shubhra Chakrabarti: Conceptualization, Validation, Investigation, Writing- Review & Editing, Supervision, Project Administration

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Tables

Tables 1 to 4 are available in the Supplementary Files section.

Figures

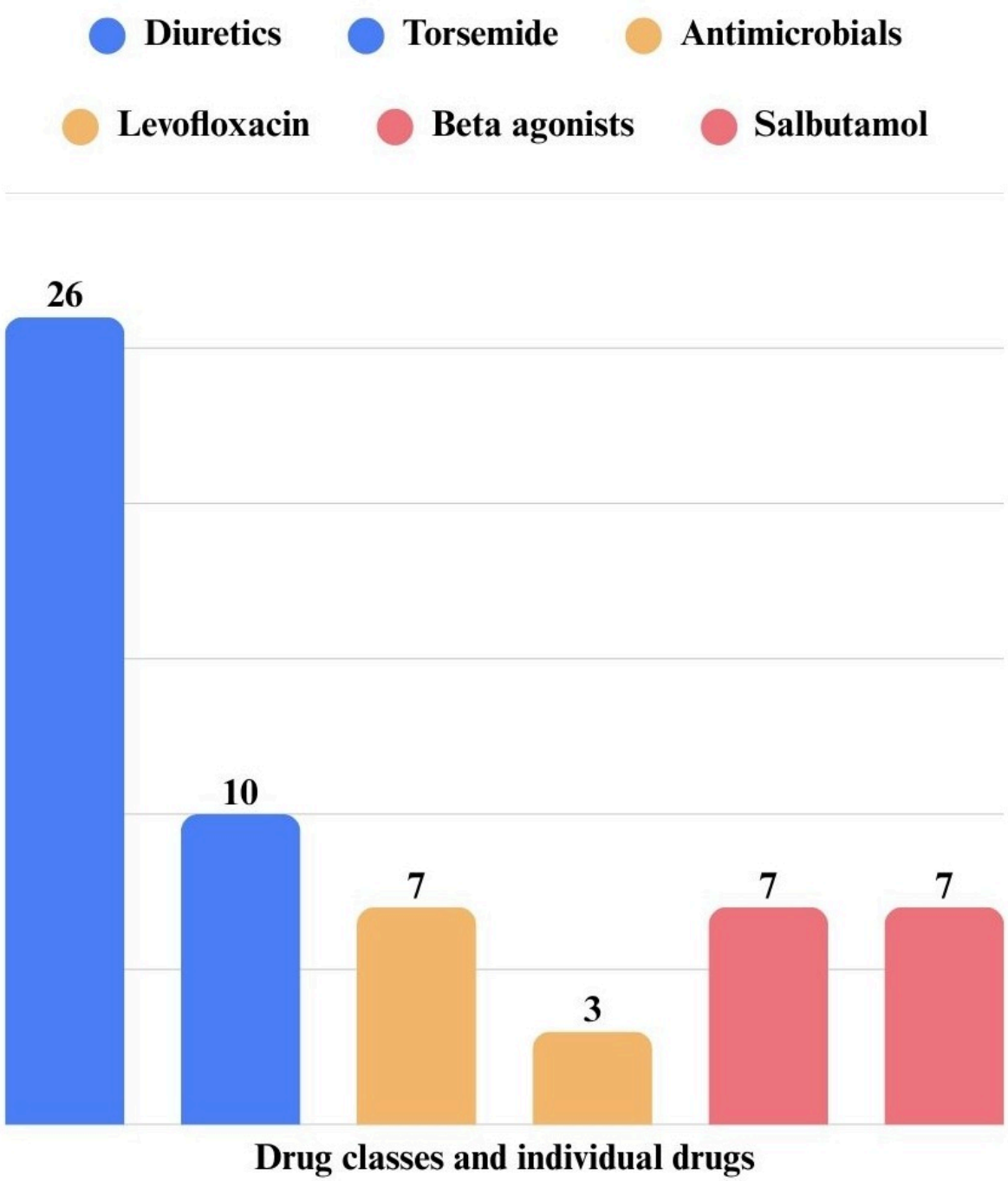


Figure 1

Common drug classes and individual drugs involved in hypokalemia.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx
- SupplementaryTable2.docx
- SupplementaryTable3.docx
- SupplementaryTable4.docx
- Table1.docx
- Table2.docx
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