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Incidence and determinants of hyperkalemia and hypokalemia in a large healthcare system

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ABSTRACT

Background: Hypo- and hyperkalemia in clinical settings are insufficiently characterized and large-scale data from Europe lacking. We studied incidence and determinants of these abnormalities in a large Swedish healthcare system.
Methods: Observational study from the Stockholm CREAtinine Measurements project, including adult individuals from Stockholm accessing healthcare in 2009 (n = 364,955). Over 3-years, we estimated the incidence of hypokalemia, defined as potassium < 3.5 mmol/L, hyperkalemia, defined as potassium > 5 mmol/L, and moderate/severe hyperkalemia, defined as potassium > 5.5 mmol/L. Kidney function was assessed by estimated glomerular filtration rate (eGFR).
Results: Of 364,955 participants, 69.4% had 1–2 potassium tests, 16.7% had 3–4 tests and the remaining 13.9% had >4 potassium tests/year. Hypokalemia occurred in 49,662 (13.6%) individuals, with 33% recurrence. Hyperkalemia occurred in 25,461 (7%) individuals, with 35.7% recurrence. Moderate/severe hyperkalemia occurred in 9059 (2.5%) with 28% recurrence. The frequency of potassium testing was an important determinant of dyskalemia risk. The incidence proportion of hyperkalemia was higher in the presence of diabetes, lower eGFR, myocardial infarction, heart failure (HF), or use of renin angiotensin-aldosterone system inhibitors (RAASi). In adjusted analyses, women and use of loop/thiazide diuretics were associated with lower hyperkalemia risk. Older age, lower eGFR, diabetes, HF and use of RAASi were associated with higher hyperkalemia risk. On the other hand, women, younger age, higher eGFR and baseline use of diuretics were associated with higher hypokalemia risk.
Conclusion: Hypo- and hyperkalemia are common in healthcare. Optimal RAASi and diuretics use and careful potassium monitoring in the presence of certain comorbidities, especially lower eGFR, is advocated.

1. Introduction

Maintenance of K+ homeostasis is important for many physiologic processes, such as cardiac electrical conduction and inotropy, smooth muscle tone, neuronal signaling and acid-base balance [1,2]. Potassium is regulated mainly in the tubuli and collecting ducts of the kidney where aldosterone stimulates its excretion. Situations that affect this pathway are thought to increase the risk of dyskalemia, including comorbidities such as chronic kidney disease (CKD), heart failure (HF), cardiovascular disease (CVD) and diabetes mellitus (DM) [3,4], as well as various common medication classes such as inhibitors of the renin-angiotensin aldosterone system (RAASi), beta blockers, calcium channel blockers and diuretics. These comorbidities are often interconnected, and medications affecting potassium homeostasis are commonly used in their treatment.

The incidence of dyskalemia in real-world clinical settings is insufficiently characterized and likely not reflected by the controlled environment of randomized controlled trials. The RALES trial, which studied

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effect of spironolactone in heart failure patients on ACEi, reported a 2% rate of severe hyperkalemia in the treatment group [5], but observational reports in the U.S. revealed that 11% of outpatients prescribed with ACEi developed hyperkalemia over a period of two years [6].

Differences in reported rates of dyskalemia may be explained by the inclusion of more heterogeneous populations [7] and diverse clinical practices, such as variations in the frequency of potassium monitoring, which is reported as suboptimal in real-world settings [8–10]. Studies with broader coverage, such as those derived from healthcare records may be relevant to inform clinical practice. Available reports in this regard are scarce and derived from North American materials [6,11,12]. Because of differences in practice patterns, drug usage and healthcare access, comparison with other countries may be useful to detect population segments where more intensive K-monitoring and/or preventive strategies are needed. In this study, we investigated the frequency, severity and recurrence of hypo- and hyperkalemia in a large Swedish healthcare system as well as comorbidities and medications associated.

2. Methods

2.1. Data sources

This project is based on the Stockholm CREAtinine Measurements (SCREAM) project [13], a healthcare-utilization cohort including all residents in the region of Stockholm, Sweden, undertaking at least one measurement of serum creatinine in inpatient or outpatient care during 2006–11. Additional laboratory data, including all serum potassium measurements in the region were extracted. Data was thereafter linked with regional and national administrative databases for information on healthcare utilization (International Classification of Diseases, Tenth Revision [ICD-10] codes and therapeutic procedures [14]), complete information of drugs dispensed at Swedish pharmacies [15], validated renal replacement therapy endpoints [16] and vital status, with no loss to follow up.

2.2. Study population

For this study, we included all individuals ≥ 18 years of age who accessed outpatient care and were registered in SCREAM between January 1st, 2009, and December 31st, 2009. Index date was set at January 1st 2009, the point at which the study covariates were calculated. An additional inclusion criterion was the existence of at least one ambulatory measurement of serum creatinine within the preceding year, in order to estimate kidney function. After applying study eligibility criteria, all available potassium measurements during the following three years were extracted until death, migration from the region or end of follow-up (December 31st, 2011). The study was approved by the Regional Ethics Review Board, Stockholm, Sweden.

2.3. Study covariates

Inter- as well as intra-laboratory variation in laboratory measurements was considered minimal among the three laboratories providing services to the region, being frequently audited for quality and harmonization by the national organization EQUALIS (www.equalis.se). The serum creatinine measured closest to index date was used to estimate glomerular filtration rate (eGFR). To this end, creatinine measurements in connection with a hospital stay were excluded, as they may represent acute illness rather than stable kidney function. Implausible serum creatinine (<25 and >1500 μmol/l) values were also excluded. All serum creatinine tests were measured with either enzymatic or corrected Jaffe methods. The 2009 CKD-EPI creatinine-based equation was used to calculate eGFR [17]. In the absence of information on albuminuria we defined eGFR categories rather than CKD stages. eGFR categories were considered as follows: G1–2 = eGFR ≥ 60 ml/min/1.73 m^2; G3 = eGFR ≥ 30 and <60 ml/min/1.73 m^2; G4+ = eGFR < 30 ml/min/1.73 m^2, also including individuals undergoing renal replacement therapy (dialysis or transplantation), which was ascertained via linkage with the Swedish Renal Registry (http://www.snronline.se).

Other covariates included age, sex, and selected comorbidities based on ICD codes (chronic kidney disease, hypertension, diabetes mellitus [DM], myocardial infarction [MI], heart failure [HF], peripheral vascular disease [PVD] and cerebrovascular disease [CeVD], see Supplemental Table S1) [12,13]. Cardiovascular disease history was defined as any event of MI, HF, PVD and CeVD. To better define diabetes and hypertension, ICD-10 codes were enriched with information on current intake of related medication (purchase of oral antidiabetics, Anatomical Therapeutic Classification [ATC] code A10; purchase of anti-hypertensives, ATC codes C03, C07, C08, C09) up to 6 months before index date.

We also extracted, at index date, information on concurrent use of medication that may affect potassium homeostasis. These included non-steroidal anti-inflammatory drugs (NSAID), renin-angiotensin-aldosterone system inhibitors (RAASi), angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor inhibitors (ARB), mineralocorticoid receptor antagonists (MRA), beta-blockers, potassium sparing diuretics, thiazide/loop diuretics, and other blood pressure medications (which included calcium channel blockers, central agonists, direct vasodilators, and α-blockers) (see Supplemental Table S2). Direct renin inhibitors were not available in Sweden during the study period.

2.4. Study outcome

The study outcomes, determined by potassium laboratory tests and defined from commonly used clinical thresholds, were: a) hyperkalemia defined as potassium > 5 mmol/L; b) moderate/severe hyperkalemia defined as potassium > 5.5 mmol/L and c) hypokalemia, defined as potassium < 3.5 mmol/L. We included all available plasma (reference range 3.5–4.4 mmol/L) and serum (reference range 3.6–4.6 mmol/L) potassium measurements in our healthcare system [18], assessed by potentiometric titration. Potassium values above 10 mmol/L were considered implausible and discarded. When more than two measurements of potassium were available in the same day, we selected their median value. Repeated tests denoting hypo-/hyperkalemia within 7 days from each other were considered as part of the same event and the date of the first abnormal potassium was used. For all outcomes, we also examined the pattern of dyskalemia over the 3-year observation period, defining patterns as never-, transient- (only 1 occurrence), or recurrent (>1 event during observation).

2.5. Statistical methods

This study utilizes actual health care data, with an indication behind each available test. Because the incidence and patterns of dyskalemia are dependent on the regularity of potassium measurements, we categorized patients by the following frequencies of testing: never, 1–2, 3–4 and >4 measurements of potassium/year, as a proxy for contact with the medical system. We used this categorization as a stratification factor in the comparisons and as a covariate in the models.

As a first step, we estimated the incidence proportion and recurrence of dyskalemias over the three-year observation period overall and in suspected populations by age strata, eGFR strata, HF, MI, DM and RAASi use. Secondly, we estimated incidence rates (IR). Adjusted IR were obtained from a zero-inflated negative binomial model and presented fixing the value of the adjustment factors to their mean value.

Logistic regression was used to examine baseline patient characteristics and medications associated with dyskalemia incidence; multinomial logistic regression was used to study patterns of dyskalemia. Covariates were selected a priori based on known associations with circulating potassium. These included age, sex, eGFR strata, comorbidities (CKD, hypertension, DM, MI, HF, PVD and CeVD) and medication

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