International Journal of Advances in Medicine
Putri LAMPD et al. Int J Adv Med. 2023 Nov;10(11):793-800
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20233211

Review Article

Hypokalemia, how to clarify and treat: a review article

Luh Ayu Made Paramita Dwisari Putri[1], Ketut Suryana[2]*

[1]Department of Internal Medicine, Wangaya General Hospital, Denpasar, Bali, Indonesia
[2]Department of Internal Medicine, Merpati Clinic, HIV and Allergy-Clinical Immunology Services Unit, Wangaya General Hospital, Denpasar, Bali, Indonesia

Received: 13 September 2023
Accepted: 07 October 2023

***Correspondence:**
Dr. Ketut Suryana,
E-mail: ketutsuryana@gmail.com

ABSTRACT

Hypokalemia is a frequent electrolyte disturbance in clinical practice and in hospitalized patients. Potassium disturbances are common and have been associated with increased mortality in several populations. The incidence of hypokalemia often occurs refractory and without a clear cause so very difficult to prevent and can increase risk of recurring conditions and require treatment. Through this overview will discuss what are the underlying causes of hypokalemia and what tests are needed to find out the cause of hypokalemia so that it can remind health worker and to prevent recurrence of emergencies conditions due to hypokalemia. The type of study is used literature review. In addition, the purpose of this study method is to reveal various theories that are relevant to the diagnostic approach to determine the causes of hypokalemia so that it can be used as reference material in daily practice. Hypokalemia is usually a sign of various diseases that can cause emergency conditions. If the cause is not known for certain, it will cause recurrent hypokalemia. It is important for health workers to conduct interviews to find out the patient's medical history, physical examination and comprehensive supporting examinations to determine the cause of hypokalemia. Comprehensive management is needed and must be done immediately so that the condition of hypokalemia does not lead to emergency conditions. In some patients, such as in endocrine related hypokalemia cases, multidisciplinary diagnostic and therapeutic approach is needed.

Keywords: Hypokalemia, Etiology of hypokalemia, Hypokalemia guide

INTRODUCTION

Potassium (K+) is one of the main intracellular cations with concentrations 30 to 40 times higher than extracellular concentrations, more than 98% of K+ is found intracellularly and only 2% extracellularly. The ratio of intracellular K+ to extracellular K+ is a major determinant of resting membrane potential and is primarily regulated by the sodium (Na+)-K+-ATPase pump located on the plasma membrane of most cells. Although extracellular K+ accounts for only 2% of total body K+, it has a major influence on ratio of extracellular and intracellular K+ via resting membrane potential. Extracellular K+ is normally regulated around a narrow range of 3.5-5.0 mmol/l.[1-3]

Changes or disturbances in K+ homeostasis can affect many organs and can cause mortality. One of the most common disturbances of K+ homeostasis is hypokalemia. Hypokalemia can be defined as a state of plasma K+ concentration of less than 3.5 mEq/L caused by various causes such as reduced total body K+ or impaired K+ ion transfer into cells. Hypokalemia is a frequent electrolyte disturbance in clinical practice and in hospitalized patients. The prevalence of hypokalemia in patients receiving hospitalization is around 14% and 40% with 5% of the patients exhibiting potassium levels below 3.0 mmol/L.[1-3] The latest data from the Nationwide Registry reports that the prevalence of hypokalemia is 3.8%. Female sex, younger age, high estimated glomerular filtration rate, and baseline use of diuretics were associated with increased hypokalemia risk. Potassium disturbances are common

and have been associated with increased mortality in several populations, such as diabetes, chronic kidney disease (CKD), and cardiovascular diseases. [1,2,4]

In some cases, the incidence of hypokalemia often occurs refractory and very difficult to prevent. It can increase risk of recurring conditions and require treatment in health facilities for emergency management of hypokalemia. Through this overview will discuss what are the underlying causes of hypokalemia and what tests are needed to find out the cause of hypokalemia so it can remind health worker and prevent recurrence of emergencies conditions due to hypokalemia.[2]

LITERATURE REVIEW

The type of study is used literature review. Literature review is a study conducted by collecting, evaluating, reviewing and critically analysing of literature such as textbooks and journals that are related to problems and research objectives. This review is contains how to establish the cause of hypokalemia. In addition, the purpose of this study method is to reveal various theories that are relevant to the diagnostic approach to determine the causes of hypokalemia so that it can be used as reference material in daily practice.

The data used in this literature review are secondary data from the results of previous research related to hypokalemia. In searching for research journal articles, the keywords "hypokalemia", "etiology of hypokalemia", and "hypokalemia guide" were used. Data collected through published journal articles include definition and prevalence of hypokalemia, potassium homeostasis, etiology of hypokalemia, diagnostic approach, and treatment of hypokalemia based on the ethology.

POTASSIUM HOMEOSTASIS

Potassium is the main intracellular cation, 98% of body K+ is found intracellularly and only 2% extracellularly. Plasma potassium is normally regulated within a narrow range of 3.5-5.0 mEq/L.[1,2,3] Normal daily K+ intake is between 60-140 mEq per day. This potassium will be excreted through the urine as much as 90% and 10% is excreted through the digestive tract. Extracellular fluid only contains K+ 60-80 mEq or 2% of the total body K+. Muscle cells contain 70% of total body K+, while liver, erythrocytes, and bones each contain about 7% of total body K+.[1,5]

K+ regulation is mediated by the Na+-K+-ATPase pump. The functions is to pump Na+ out of the cell and pull K+ into the cell, thereby creating a greater intracellular K+ gradient than extracellular K+ to maintain potential differences between membranes that function in some cells. Intracellular potassium plays an important role in acid-base regulation through the exchange of extracellular hydrogen ions (H+) by influencing the rate of kidney amnion production. Counterregulatory mechanisms are used to defend against changes in K+, maintain the proper distribution of K+ in the body and regulate the total K+ content of the body. Hyperkalaemia will lower the membrane potential, while hypokalemia will cause hyperpolarization and unresponsiveness of the membrane. Disturbance in K+ balance can cause disturbances in the heart's electrical conduction and even sudden death.[2.3,5]

Potassium predominates intracellularly where it is the most abundant cation and involved regulation and several cellular processes. The fraction of K+ in the extracellular fluid is so small so that plasma or serum levels are not useful indicators of total body K+ stores. K+ homeostasis is maintained through a combination of adjustments in acute cellular shifts between extracellular and intracellular fluid compartments, renal excretion, and to a lesser extent gastrointestinal losses. Potassium which is rapidly absorbed by the intestine, can significantly increase serum K+ but several physiological mechanisms rapidly shift K+ to intracellular, liberating slow excretion of K+ by the kidneys, and maintenance of normal K+ homeostasis.[1,5]

Kidney is the main route of K+ excretion and responsible for maintaining total body K+ balance. Therefore, the kidney is responsible for long-term K+ homeostasis as well as serum K+ concentration. In the short term, serum K+ is also regulated by the movement of K+ between the intracellular and extracellular compartments.[1,3]

Transport mechanism of potassium in kidney

The main segments of the nephron are the proximal convoluted tubule, loop of Henle with thin and thick limbs, distal convoluted tubule, and collecting ducts consisting of connecting tubules, cortical collecting ducts (CCD), and medullary collecting ducts. The collecting ducts consist of two types of the cells, principal cells which reabsorb the Na+ and secrete K+ under the influence of aldosterone, and intercalating cells which maintain the acid-base balance.[1,5]

Potassium filtered through the glomerulus is almost completely absorbed before it reaches the collecting ducts. About 65% is absorbed in the proximal tubule and 25% in the loop of Henle. About 10% of filtered K+ reaches the early distal tubule. The final amount of K+ excreted in the urine is mainly controlled by the late distal convoluted tubules, connecting tubules, and CCD.[5]

There are several types of the K+ channels in the kidney and other organs. Two types of the K+ channels are found in the CCD, including: (1) Renal Outer Medullary Potassium Channel (ROMK) is the main K+ secretory channel and is activated by aldosterone. It is located in the principal cell of CCD and under physiological circumstances, it has a high probability of opening and (2) Maxi K+ Channel is one of the highest conductance K+ channels activated at a high flow rate through the collector channel. Maxi K+ channels contribute to the increased flow-dependent K+ secretion.[3,5]

Aldosterone is secreted by the zona glomerulosa of the adrenal cortex. It is a major determinant of K+ secretion. Aldosterone as the main regulator of renal K+ homeostasis binds to mineralocorticoid receptors in the distal tubule and main cells in CCD. Aldosterone increases Na+ uptake and K+ excretion through activation of the Na+-K+-ATPase pump and increases the number of K+ channels that open thereby increasing the reabsorption of Na+ and water into the blood and the secretion of K+ into the urine. The Na+-K+-ATPase pump is located on the basolateral membrane of the principal cells and present in almost all living cells. Aldosterone also increases the amiloride sensitive sodium channels (ENaCs) in the apical membrane of the CCD and stimulates the secretion of H+ ions by the intercalated CCD cells, thereby affecting the acid-base balance.[5,6]

Extrarenal potassium regulation mechanism

Acid-base Balance

Acid-base balance can affect the balance between intracellular and extracellular K+ concentrations. Intracellular potassium participates in acid-base regulation by exchanging extracellular H+ ions and by influencing the rate of renal ammonium production. Counterregulatory mechanisms exist to defend against changes in K+. This mechanism serves to maintain the proper distribution of K+ in the body, as well as to regulate the total body K+ content. Excessive extracellular K+ (hyperkalaemia) reduces membrane potential, whereas hypokalemia causes hyperpolarization and unresponsiveness of the membrane. An acidotic state can increase plasma K+ concentration by inducing a shift of K+ to extracellular compartment in exchange for H+, and also cause a decrease in tubular K+ secretion. Conversely, a state of alkalosis will cause a shift of K+ to intracellular compartment, causing hypokalemia.[2,3]

The effects of acid-base status are much more complicated and depend on the nature of the disorder. Although practically, for every 0.1 unit change in pH there is a 0.6 mmol/l change in serum K+. For example non-organic acidosis, such as acidosis in renal failure, has a large effect on the K+ shift. Meanwhile, organic acidosis as seen in diabetic ketoacidosis or other acid-base disturbances have minimal effect.[2]

Insulin dan catecholamine

Insulin has an important role in preventing large changes in extracellular fluid K+ concentration because it enhances K+ uptake into the liver and muscle cells by stimulating Na+-K+-ATPase. Large increases in extracellular fluid K+ concentration (>1–1.5 mmol/l) stimulate insulin secretion, which promotes a shift of excess K+ into the intracellular compartment. Normal physiological regulators of insulin and catecholamines, stimulated by the consumption of foods containing glucose and K+. This hormone is important in shifting intracellular K+ and storing it primarily in the liver and striated muscle cells. Catecholamines can cause an intracellular shift of K+ through activation of Beta 2-receptor agonists. [1,3,5]

DEFINITION OF HYPOKALEMIA

Hypokalemia is a state of plasma K+ concentration below 3.5 mEq/L caused by a reduced total body K+ amount and a disturbance in the movement of K+ ions into cells. [1,7,8,9] The prevalence of hypokalemia is 2 times more in female than in male. [1,5] A study of 8000 patients in the emergency department found 39% with hypokalemia and 20% of all patients who were hospitalized were found with hypokalemia.[5] Recent studies have shown that hypokalemia involve a higher risk arrhythmia and cause mortality.[4]

ETIOLOGY OF HYPOCALEMIA

In general, hypokalemia can occur as a result of increased K+ loss through the skin, gastrointestinal tract, and kidneys, transcellular shifts due to increased intracellular absorption because of use drugs that can reduce K+ levels and hormonal disorders, and decreased K+ intake which is common in patients with dementia and anorexia.[1,2,5,10] Decreased K+ intake rarely causes hypokalemia because of the kidney's ability to effectively minimize K+ excretion. However, reduced intake can be a contributor to hypokalemia in the presence of other underlying causes such as malnutrition, diuretic therapy, renal impairment, metabolic, and digestive disorders.[3,5] Increased intracellular absorption of K+ is stimulated by several things such as alkalemia, insulin, beta-adrenergic stimulation, aldosterone and xanthine. Most cases of hypokalemia are caused by gastrointestinal (GI) or renal disorders. Increased delivery of Na+ and/or nonabsorbable ions (as in diuretic therapy, magnesium deficiency, and genetic syndromes) to the distal nephron can also lead to renal K+ wasting. Gastrointestinal losses such as severe diarrhea and persistent vomiting are the most common causes of hypokalemia.[1,2,7]

Loss

Renal loss

Loss of K+ from the kidneys is a major cause of hypokalemia. Conditions that can cause this include use of drugs such as diuretics, hyperaldosteronism, glucocorticoid-remediable congenital adrenal hyperplasia, hypomagnesemia, renal tubular acidosis, and genetic disorders.[2,5,7]

Drugs that can cause K+ loss through the kidneys such as diuretics, antibiotics, foscarnet, and cisplatin.[11] One of the most common causes of hypokalemia is the use of diuretics. Loop and thiazide diuretics increase the supply of Na+ to the collecting ducts which induces its reabsorption and creates an electrochemical gradient that enhances K+ elimination. The combination of more than

one of diuretics, such as loops with a thiazide, can also induce hypokalemia.[1,2,5,7]

Loop diuretics work by inhibiting the Na+-K+-Cl co-transporter. These drugs also inhibit magnesium and calcium reabsorption by reducing the potential difference between the tubular lumen and the interstitial (the main driving force for ion reabsorption in these segments). Use of loop diuretics can also increase urinary K+ excretion caused by various mechanisms including (1) Increasing the supply of Na+ especially to the collecting ducts, intensifying the excretion of K+ and H+ (Na+ reabsorption by main cells creates an electrochemical gradient that allows K+ secretion into the tubular lumen, through ROMK channel); (2) Activation of the renin-angiotensin-aldosterone system (RAAS) due to dehydration and decreased sodium-chloride (NaCl) transport in the dense macula; (3) Release of vasopressin, in response to Na+ and volume depletion.[3]

Increased aldosterone levels (hyperaldosteronism) can induce hypokalemia. Aldosterone activates ENaC channels in principal cells through various mechanisms, thereby stimulating the Na+-K+-ATPase pump to excrete K+ with the consequent increase in Na+ retention and K+ secretion.[2,3,6]

Glucocorticoids such as hydrocortisone, prednisone, and prednisolone do not directly interfere with renal K+ excretion. Glucocorticoids usually have the potential to cause hypokalemia when administered at doses that produce minimal mineralocorticoid stimulation.[2,3] Mineralocorticoid excess such as with long-term use of fludrocortisone, can induce K+ depletion in the distal nephron, through its action on mineralocorticoid receptors which stimulate expression and activity of the Na+-K+-ATPase pump, ENaC, and ROMK channels, inducing Na+ reabsorption and K+ secretion.[3]

Magnesium depletion can cause refractory hypokalemia because magnesium deficiency has an inhibitory effect on Na+/K+-ATPase activity, reducing K+ influx into muscle cells and causing secondary caliuresis. In addition, magnesium depletion causes excessive K+ secretion by the distal nephron. Consequently, patients with hypomagnesemia may be clinically refractory to K+ replacement if magnesium levels are not corrected. It is very important to check magnesium levels to rule out hypokalemia caused by hypomagnesemia.[3,5]

Several genetic disorders such as Bartter syndrome and Gitelman syndrome can cause hypokalemia. Gitelman syndrome is classified as an autosomal recessive hereditary tubulopathy caused by a mutation in the SCL12A3 gene located on the long arm of chromosome 16 (16q13).[11-13]

Renal tubular acidosis is a condition that can cause hypokalemia through renal loss. Distal renal tubular acidosis (dRTA) is characterized by a failure to acidify the urine that occurs in the distal portion of the nephron, including the connecting tubules and collecting ducts.[14]

Antibiotics can cause hypokalemia such as amphotericin B, penicillin, aminoglycosides and capreomycin. Beta-lactam antibiotics such as penicillin can cause renal K+ loss when given intravascularly and in high doses, by increasing the supply of Na+ to the distal segments of the nephron. Treatment with amphotericin B can result in hypokalemia and hypomagnesemia in up to 90% of cases, depending on the dose administered. Several mechanisms have been associated with amphotericin B-induced electrolyte disturbances such as changes in the Na+-K+-ATPase pump in the distal tubule, and increased absorption of Na+ in the gastrointestinal tract, with resultant excretion of K+ in the feces.[3,15]

Non renal loss

The most common cause of K+ loss is through gastrointestinal loss including: diarrhea, vomiting, naso-gastric tube (NGT) suction and use of laxatives and enemas. The direct loss of K+ in diarrhea that occur persistent is very important to note because the concentration of K+ in the stool is quite high around 80-90 mEq/L. Under conditions of use of laxative drugs for bowel emptying can potentially cause hypokalemia. Continuous vomiting and suctioning of the NGT can also cause hypokalemia due to secondary hyperaldosteronism (due to dehydration).[1,2,5,7]

Intracellular shifting

Drug-induced intracellular shifting

Insulin and Beta 2-receptor agonists (such as albuterol, and ephedrine) are the main causes of the intracellular shift of K+. While other drugs that can also cause a shift in K+ to intracellular are xanthin groups, verapamil, barium caesium, chloroquine and antipsychotic drugs.[2,3]

Insulin (high doses/overdose)

The physiological response of insulin is to activate the Na+-K+-ATPase channel pump and push K+ rapidly into the cell. At normal levels, insulin will only induce a temporary decrease in serum K+ concentration which will be normalized by a gradual release of K+ back into plasma. However, high-dose insulin levels, for example in dosage errors and advanced stage or during the treatment of diabetes mellitus, can cause hypokalemia.[2,3,5]

Beta 2-receptor agonist

Beta 2-receptor agonists are a group of drugs other than insulin that promote activation of the Na+-K+-ATPase pump. Beta 2-receptor agonist drugs that can induce hypokalemia are drugs commonly used to treat asthma, such as antispasmodic agents and bronchodilators (albuterol, terbutaline, ephedrine, isoproterenol, fenoterol,

pirbuterol), decongestants (pseudoephedrine), tocolytics (ritodrine and nilidrine), dopamine, and dobutamine.[1,3,5,7] Beta 2-receptor agonist-induced hypokalemia can persist for several hours and may reach as low as 2.5 mEq/L depending on the dose and route of administration. [3,5]

Verapamil overdose

Therapeutic doses of antiarrhythmic agents, as verapamil, do not increase risk of hypokalemia. However, taking high doses of verapamil can cause severe hypokalemia.[3]

Antipsychotic drugs (risperidone dan quetiapine)

The mechanism of hypokalemia induced by the antipsychotic drugs quetiapine and risperidone is still unclear. One possible mechanism is the aldosterone and catecholamine effects of antipsychotic drugs.[16]

Non drug-induced intracellular shifting

An acute anabolic state in which intense stimulation from growth factors, colony stimulating factors, and other mediators promotes cell proliferation and K+ shifts from the extracellular to the intracellular environment where formation can occur. Some conditions that can cause hypokalemia in this context are metabolic alkalosis, advanced lymphoma, and treatment of anaemia due to B12 deficiency. Metabolic alkalosis can cause hypokalemia due to loss of H+ and increase in bicarbonate.[3]

Other conditions that can cause severe hypokalemia include hyperthyroidism or thyrotoxicosis in Graves' disease where hypokalemia occurs because of the rapid and massive shift of K+ from the extracellular to the intracellular compartment due to thyroid hormone stimulating Na+-K+ ATPase transcription, and increasing the activity of these pumps and membranes in skeletal muscle cells. The hypokalemia state of hyperthyroidism can lead to periodic attacks of hypokalemic paralysis (thyrotoxic periodic paralysis).[1,3,5]

Other causes

Pseudohypokalemia

Pseudohypokalemia is a state of false hypokalemia with high K+ levels and can be observed in severe thrombocytosis (>500,000/mm^3) caused by myeloid proliferative disorders. Inaccurate serum or plasma K+ values may occur in conditions such as acute leukemia or there is a delay in the transport of blood samples due to excessive K+ uptake by metabolically active cells, particularly by the white blood cell mass.[5,17]

Decreased potassium intake

Basically, K+ intake does not significantly increase plasma K+. Theoretically, an intake of 35 mEq K+ will increase plasma K+ levels by 2.5 mEq/l if the total distribution is extracellular. However, in reality, only about a quarter of K+ intake remains extracellular, due to storage in muscle cells, liver, and red blood cells as a buffer. Thus, a decrease in K+ intake does not have a significant effect on the incidence of hypokalemia except in conditions of extreme decreased potassium intake such as in dementia patients with anorexia or eating disorders such as bulimia nervosa.[1,5,18]

Table 1: Etiology of hypokalemia.

Loss	Intracellular shifting	Other conditions
Renal loss Drug-induced renal loss: Loop diuretics Antibiotics (Penicillin G, Nafcillin, Amphotericin B, Aminoglycosides) Foscarnet Cisplatin Glucocorticoid and mineralocorticoid Non drug-induced renal loss: Hyperaldosteronism Hypomagnesemia Renal tubular acidosis Adrenal hyperplasia/carcinoma Genetic disorders: Gitelman syndrome, Bartter syndrome and Liddle syndrome **Non renal loss:** Gastrointestinal Loss: diarrhea, vomiting Drug induce: Laxatives, enema	**Drug-induced intracellular shifting** Insulin Beta 2-receptors agonist Verapamil overdose Anti-psychotic (Risperidone and Quetiapine) **Non-drug-induced intracellular shifting** Hyperthyroidism Vitamin B12 deficiency Lymphoma	Pseudohypokalemia Low intake of K+

DIAGNOSTIC APPROACH

Medical history finding

Diagnostic approach through history taking is very important to find the cause of hypokalemia. Things to look for from the patient's history such as persistent or long-term dehydration, diarrhea and vomiting, use of drugs such as laxatives, antibiotics, diuretics, beta 2-receptor agonists, and insulin. Other important things that need to be known from the patient's history are history of chronic disease such as kidney disorders, tumors in the adrenal glands, family history, and other risk factors that exist in patients such as low intake, for example in the elderly with dementia and anorexia.[5,7]

Physical examination finding

Potassium plays an important role in the physiology of various tissues, organs and systems. If there is a disturbance, it can cause changes in cardiovascular function, skeletal muscle, kidneys, and have an effect on the release of certain hormones. A comprehensive physical examination needs to be carried out to determine if there are any symptoms associated with etiology of hypokalemia such as nausea, vomiting, abdominal distention and diarrhea associated with gastrointestinal disorders. Several cases of hypokalemia are often found asymptomatic, especially in chronic or persistent hypokalemia.[1,3,5] Patients with hyperthyroidism can generally find symptoms such as tremors, enlargement of the thyroid gland, and also drastic weight loss which can also be found in anorexic patients. Nocturia and polyuria may occur, especially in the persistent hypokalemia, such as those with Bartter as well as the Gitelman syndrome.[2,5,7,13]

Hypokalemia can induce neuromuscular symptoms such as muscle weakness (periodic paralysis) with characteristics of weakness in the lower extremities which can progress to the trunk and upper extremities to paralysis including paralysis of the respiratory muscles. The hyperpolarization of skeletal muscle that occurs in hypokalemic conditions compromises its ability to depolarize and contract. In addition, a dehydrated state (e.g., during diabetic ketoacidosis) can reduce blood supply to muscles and induce rhabdomyolysis. Together these processes can cause muscle weakness and the fatigue.[19,20]

Supporting examination

Several investigations are needed to evaluate the severity of hypokalemia, determine the underlying cause and to start effective treatment. Basic biochemical laboratory tests (including routine hematology, serum glucose, sodium, potassium, chloride, blood gas analysis, urea, creatinine, magnesium, and calcium) are the cornerstone of screening in patients with hypokalemia.[1,2,10]

The major cardiovascular change is cardiac arrhythmia. The serious arrhythmias that can be induced by hypokalemia are ventricular tachycardia and fibrillation.[8] Low K+ concentrations increase cardiac muscle excitability and delay the repolarization, which can induce arrhythmias.[3,7] ECG test is needed to see the risk of arrhythmias. ECG manifestation of hypokalemia is decreased T-wave amplitude, ST-interval depression, T-wave inversions, and U waves. Although the risk of ECG changes and arrhythmias increases as serum potassium concentration decreases, but some patients do not have ECG changes.[2,7,10,20]

Tests and the imaging of the endocrine glands are relevant, but these should not be first line tests. The computerized tomography (CT) or the magnetic resonance imaging (MRI) may be done if there is suspicion of the mineralo-corticoid, glucocorticoid and/or the catecholamine excess.[10]

In patients who have signs and symptoms of hypokalemia with serum K+ less than 3 mmol/L, it is important to carry out a sequential analysis of the possible causes and mechanisms of hypokalemia. In general, there are two main components of a diagnostic evaluation if the cause of hypokalemia cannot be known. (1) 24-hour urinary K+ excretion to differentiate renal K+ loss from other causes of hypokalemia, (2) Assessment of acid-base status, some cases are associated with metabolic alkalosis or acidosis, and (3) Other additional tests such as screening tests for aldosteronism, urine diuretic screening, and thyroid function are performed especially in refractory hypokalemia.[1,2,7]

Examination of 24-hour Urine K+ Levels is useful for differentiating causes of renal and non-renal hypokalemia. If the hypokalemia is due to gastrointestinal losses, the kidneys retain K+ and the 24-hour urine K+ level is <30 meq. In patients with hypokalemia due to renal loss, the 24-hour urinary K+ level is ≥ 30 meq.[2,5,7,21]

Examination of Urine Potassium and Creatinine Ratio is use if a 24-hour urine K+ test cannot be performed, a measurement of the urine K+ to creatinine ratio obtained in a random specimen can be performed. If hypokalemia is caused by renal loss, the ratio of K+ in mmol to creatinine in mmol is > 1.5. Renal failure is diagnosed if the ratio of K+ in mEq to creatinine in g >13, and if the ratio K+ to creatinine is less than 1.5 its possible cause by gastrointestinal losses, intracellular shift, or other conditions.[3,5]

Screening for primary aldosteronism (PA) is recommended for any case with hypokalemia and hypertension induced spontaneously or by diuretics. In such cases, the plasma aldosterone to plasma renin activity ratio should be assessed. If it is higher than 20, further confirmatory tests such as oral Na+ test, saline infusion test, fludrocortisone suppression test are no longer needed.[2,5,6]

For confirmation, in the case of patients with hypertension, who are at high risk for primary hyperaldosteronism, hypertension with incidental adrenaloma, and a family history of early onset hypertension or cerebrovascular accident), should be examined for the ratio of plasma aldosterone concentration to plasma renin activity. Adrenal computerized tomography scan is recommended in all patients with PA. Genetic testing for glucocorticoid-remediable aldosterone (GRA) is recommended in patients with confirmed PA starting before age 20 years old or with a family history of PA.[2,6]

Arterial blood gas (ABG) analysis should be performed to detect metabolic acidosis or alkalosis. It also useful to choose appropriate strategy of potassium supplementation in case of acidosis or alkalosis.[2]

Assessment of free thyroxine (FT4) and thyroid-stimulating hormone (TSH) levels are necessary in cases of tachycardia or clinical suspicion of hyperthyroidism. It can help to diagnose thyrotoxic periodic paralysis (TPP) with limb weakness or paralysis.[20]

Serum magnesium, calcium and phosphorus levels are important to exclude associated electrolyte abnormalities.[2] If hypokalemia due to diuretic use is suspected, a urine diuretic screening should be performed. A clue to diuretic abuse is inconsistent random urine K+ and creatinine ratio values (levels will be high while taking the diuretic, and levels will be low several hours after last diuretic dose).[5]

MANAGEMENT

The goal of therapy for hypokalemia is to prevent or treat life-threatening complications, replace the K+ deficit, replenishment of potassium stores, evaluation for potential toxicities and correct the underlying cause. The urgency of therapy depends on the severity of hypokalemia, the presence of comorbid conditions, and the rate of decrease in serum K+ levels.[1-3]

There are three main steps that need to be considered for the management of hypokalemia, including: (1) identifying and treating the underlying cause, (2) reducing and preventing further K+ loss according to the underlying cause such as avoiding laxatives, preventing or stopping vomiting or diarrhea, change using thiazides with the lowest possible if diuretic therapy is needed, (3) Replenishment of K+ stores.[1]

Most patients with hypokalemia will be given replacement of serum K+ with K+ chloride (KCl). Potassium chloride is available in many types of preparations such as extended-release tablets, capsules, liquids and intravenously). Potassium chloride acts quickly and is used more frequently, especially in patients with metabolic alkalosis.[5]

Patients with mild hypokalemia with serum K+ of 3.0-3.5 mEq/l are treated with oral K+ preparations such as KCl, potassium citrate, and potassium phosphate. As long as the patient is in a condition that allows oral administration, oral KCl can be given at a dose of 60 to 80 mmol/day in divided doses over several days to weeks. In addition to oral potassium supplementation, a high K+ diet by consuming more vegetables and fruits that have high K+ levels are needed.[1,5]

Indications for intravenous administration of KCl are moderate to severe hypokalemia (serum K+ levels <3 mEq/l), especially in emergency situations such as arrhythmias, neuromuscular dysfunction, and respiratory failure. Intravenous (IV) KCl correction may also be given if oral therapy is not tolerated. Intravenous KCl can be given at a rate of 10 mEq/hour. KCl replacement therapy at a rate of 20 mEq/hour can be given in severe hypokalemia with an emergency situation. If K+ serum <2.5 mmol/L and/or critical symptoms, intravenous KCl can be given via a central vein at a rate of 10-20 mmol/hour. Serial monitoring of ECG and K+ levels should be performed to prevent hyperkalemia.[1,5,7] KCl will increase serum K+ levels by an average of 0.25 mmol per hour. Higher rates of using a central venous catheter (up to 40 mmol/hour or 2 mmol/minute for 10 minutes, followed by 10 mmol over 5-10 minutes) have been shown to be successful in hypokalemic emergency settings. Giving KCl via rapid intravenous is not allowed because it can cause cardiac arrest. Serum K+ levels should be checked every 2 to 4 hours. K+ repletion may occur more slowly after serum K+ levels are persistently above 3 mmol/L or clinical symptoms have resolved.[1,5]

In the state of hypokalemia with hypomagnesemia, it is necessary to correct magnesium deficiency simultaneously. Hypomagnesemia is common in hypokalemic patients, especially those treated with loop diuretics or thiazides. In such cases, K+ levels will not return to normal until the hypomagnesemia is corrected.[1]

For hypokalemia associated with diuretic use, stopping the diuretic or reducing its dosage may be effective. Another strategy, if otherwise indicated to treat a comorbid condition, is use of an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), or potassium-sparing diuretic because these drugs is associated with an elevation in serum potassium.[7]

CONCLUSSION

Hypokalemia is usually a sign of various diseases. The occurrence of hypokalemia can cause emergency conditions such as arrhythmias and if the cause is not known for certain, it will cause recurrent hypokalemia. Therefore, it is important for health workers to conduct interviews to find out the patient's medical history, physical examination and comprehensive supporting examinations to determine the cause of hypokalemia. There are two major components for the diagnostic evaluation: (a) assessment of urinary potassium excretion in order to distinguish renal potassium losses from the

other causes of hypokalemia, and (b) assessment of acid-base status, since some causes of hypokalemia are associated with metabolic alkalosis or metabolic acidosis. The renal potassium excretion is better assessed by a 24-h urine collection. Once the cause is known, management can be carried out according to the cause so that recurrent hypokalemia can be prevented. Comprehensive management is needed to prevent emergency conditions of hypokalemia. Potassium should be gradually replaced, preferably by oral administration if clinically feasible. In cases of severe/symptomatic hypokalemia and cardiac complications, IV administration with serial ECG monitoring is recommended. In some patients, such as in endocrine related hypokalemia cases, multidisciplinary diagnostic and therapeutic approach is needed.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Krogager ML, Kragholm K, Thomassen JQ, Sogaard P, Lewis BS, Wassmann S et al. Update on Management of Hypokalemia and Goals for The Lower Potassium Level in Patients with Cardiovascular Disease: A Review In Collaboration with The European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy. Eur Heart J. 2021;7:557-67.
2. Kardalas E, Paschou SA, Anagnostis P, Muscogiuri G, Siasos G, Vryonidou A. Hypokalemia: a clinical update. Endocrine Connections. 2018;7:R135-46.
3. Ring LC, Nishide KG, Rangel EB. Hypokalemia in Diabetes Mellitus Setting. Medicina. 2022;58(431):1-18.
4. Vuillaume VA, Ferreira JP, Asseray N, Paviot BT, Montassier E, Legrand M et al. Hypokalemia is Frequent and has Prognostic Implications in Stable Patients Attending the Emergency Department. PLOS one. 2019;15(8):1-13.
5. Tinawi M. Hypokalemia: A Practical Approach to Diagnosis and Treatment. Arch Clin Biomed Res 2020;4(2):048-66.
6. Kai K, Tominaga N, Uchida D, Fukai N, Matsuura Y, Uda S et al. Aldosterone Response in Severe Hypokalemia and Volume Depletion: A Case Report and Review of the Recent Research. Hindawi Publishing Corporation 2016: 1-6.
7. Viera AJ, Wouk N. Potassium Disorders: Hypokalemia and Hyperkalemia. Am Family Physician. 2015;92(6):487-95.
8. Kyaw MT, Maung ZM. Hypokalemia-Induced Arrhythmia: A Case Series and Literature Review. Cureus 2022;14(3):22940.
9. Palmer BF, Clegg DJ. Physiology and Pathophysiology of Potassium Homeostasis: Core Curriculum 2019. Am J Kidney Dis. 2019;74(5):682-95.
10. Setiawan I, Wirawan IMS. Refractory Hypokalemia: A Case Report. Int J Adv Med. 2022;9(11):1115-9.
11. Urbano JlZ, Truque AED, Chaparro JMO, Florez XC. Gitelman Syndrome, A Rare Cause of Refractory Hypokalemia. A Case Report. Revista de la Facultad de Medicina. 2020;7(1):1-7.
12. Blanchard A, Bockenhauer D, Bolignano D, Calo LA, Cosyns E, Devuyst O et al. Gitelman Syndrome: Consensus and Guidance From A Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2017;91:24-33.
13. Shahzad MA, Mukhtar M, Ahmed A, Ullah W, Saeed R, Hamid M. Gitelman Syndrome: A Rare Cause of Seizure Disorder and a Systematic Review. Hindawi Case Rep Med. 2018;1-8.
14. Rios GV Jr, Philip I, Edwards JC, Shieh S. Distal Renal Tubular Acidosis and Severe Hypokalemia: a case report and review of the literature. J Med Case Rep. 2019;13(103):1-7.
15. Casado F, Mudunuru SA, Nasr R. A Case of Hypokalemia Possibly Induced by Nafcillin. Antibiotics. 2018;7(108): 1-5.
16. Yang Q, Guo X, liu D. Hypokalemia Caused by Quetiapine and Risperidone Treatment in Schizophrenia: A Case Report. Shanghai Arch Psychiatr. 2018;30(3):204-06.
17. Sathick J, Shaikh A. Pseudo-Electrolyte Disorders in Patients with Cancer: When seeing is not Believing. ASN Kidney News. 2022: 21.
18. Oliviera J, Freitas J, Sala I, Tavares J, Santos S, Cabrita A. Diet and Exercise Induced Hypokalemia. Nefrologia. 2022;12(010).
19. Lien YHH. Paradoxical Hypokalemia: Where has All The Potassium Gone? Am J Med. 2015;128(3):217-18.
20. Pinzon RT, Wijaya BM, Japanto E. Sudden weakness due to thyrotoxic periodic paralysis: a case report. J Med Sci. 2022;54(1):57-62.
21. Chhabria M, Castillo IP, Chowdbury M, Sohail A, Tejera DS, Bress J et al. A Case of Severe Hypokalemia. Am J Kidney Dis. 2020;76(1):A9-12.

Cite this article as: Putri LAMPD, Suryana K. Hypokalemia, how to clarify and treat: a review article. Int J Adv Med 2023;10:793-800.