Review Article

Potassium Homeostasis, Oxidative Stress, and Human Disease

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Abstract

Potassium is the most abundant cation in the intracellular fluid, and it plays a vital role in the maintenance of normal cell functions. Thus, potassium homeostasis across the cell membrane is very critical because a tilt in this balance can result in different diseases that could be life-threatening. Both oxidative stress (OS) and potassium imbalance can cause significant adverse health conditions. OS and abnormalities in potassium channel have been reported in neurodegenerative diseases. This review highlights the major factors involved in potassium homeostasis (dietary, hormonal, genetic, and physiologic influences), and discusses the major diseases and abnormalities associated with potassium imbalance including hypokalemia, hyperkalemia, hypertension, chronic kidney disease, and Gordon's syndrome, Bartter syndrome, and Gitelman syndrome.

Keywords: Differential diagnosis, hyperkalemia, hypokalemia, oxidative stress, potassium excretion, potassium homeostasis

Received: 03rd September, 2017; ***Revised:*** 14th September, 2017; ***Accepted:*** 20th September, 2017

Introduction

Electrolyte balance is important for general functioning of the body, and it is closely monitored in clinical settings because electrolytic abnormalities are caused by a wide variety of factors and may lead to a wide variety of disorders. The most common electrolytes in the body are sodium, potassium, and chloride that are often measured in the laboratory using ion-selective electrodes technology. Maintenance of the balance between water and electrolyte composition of the body in a healthy individual requires specific stringent homeostatic mechanisms. Water constitutes 60% of the lean body mass, and it is described in terms of intracellular fluid (ICF) and extracellular fluid (ECF). ECF includes the fluid inside blood cells and blood plasma. A constant osmotic equilibrium is maintained between the ICF and ECF, however, their electrolyte composition differs. ECF contains mostly sodium cations while the ICF has an abundance of potassium cations primarily in muscles.[1-4] However, about 2% of the total body potassium can be found in the ECF. In a normal healthy person, the plasma potassium is maintained within a narrow range of 3.5–5.0 mEq/L.[5]

Potassium homeostasis involves redistribution of potassium between cells ICF and the ECF. The control of the movement of potassium from intracellular to extracellular space is one of the ways that the body's potassium balance is maintained. The body has a way to maintain this balance for example, when potassium is lost through the renal system, the body pushes out cellular potassium which prevents the expected drop in plasma potassium level. Potassium intake, renal excretion, and loss through the gastrointestinal tract are crucial in potassium homeostasis.[6]

Potassium homeostasis is highly influenced by the activities of the sodium and potassium pump (Na^+-K^+-ATPase) which facilitates the active transport of sodium and potassium ions across the cell membrane against their concentration gradients. The Na^+-K^+-ATPase is found in the membrane of almost all animal cells, and it pumps sodium ions (Na^+) out of the cell and potassium ion (K^+) into the cell. This pump keeps the K^+ - balance between the ICF and ECF primarily through a buffering that involves hydrolysis of ATP to generate energy,

Access this article online

Quick Response Code:

Website: www.ijcep.org

DOI: 10.4103/ijcep.ijcep_43_17

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How to cite this article: Udensi UK, Tchounwou PB. Potassium homeostasis, oxidative stress, and human disease. Int J Clin Exp Physiol 2017;4:111-22.

and for each ATP hydrolyzed, two K^+ are transported inside while three Na^+ are pushed out of the cell. This maintains high Na^+ in the ECF and high K^+ in the ICF and creates an electrical gradient.[7] The cytoplasm becomes negatively charged as the number of Na^+ leaving the cell is higher than the number of K^+ entering the cell (i.e., more positive charged ions leave the cell). This electrical gradient is used in neurons and muscles for nervous system function and muscular contraction.[8] This K^+ and Na^+ interchange influences K homeostasis. When the body needs to retain more Na^+, renal K^+ secretion is induced leading to an increase in the delivery and reabsorption of Na^+ by the distal nephron. This conversely forces the passive K^+ efflux across the apical membrane.[9]

Apart from K^+ loss through the renal system, extrarenal mechanisms also affect the normal potassium homeostasis. Extrarenal mechanism includes potassium uptake by both liver and muscle generally and intestinal secretion of potassium. Extrarenal tissues regulate acute potassium tolerance while the kidneys manage chronic potassium balance. Several hormones, including insulin, epinephrine, aldosterone, and glucocorticoids are involved in the maintenance of normal extrarenal potassium metabolism.[10] These hormones enhance potassium uptake by the liver and muscle. The in and out of cell movement of potassium could be also affected by changes in acid–base balance.[11] This depends on the exchange of hydrogen ions for potassium across the cell membrane. A shift of H^+ out of the cell and potassium into the cell occurs when there is an increase in serum pH (decrease in H^+ concentration). Conversely, under acidic condition (acidemia), a shift of potassium out of the cell occurs. A significant rise in serum potassium may result from a sudden increase in plasma osmolality which shifts water out of the cell and drags in some potassium with the water.[12] A screenshot of the major conditions associated with potassium imbalance which causes different health abnormalities and diseases is shown in Figure 1, and these conditions include hypo and hyperkalemia, pseudohyperkalemia, and pseudohypoaldosteronism.[13-17] They are discussed more in detail later in this review.

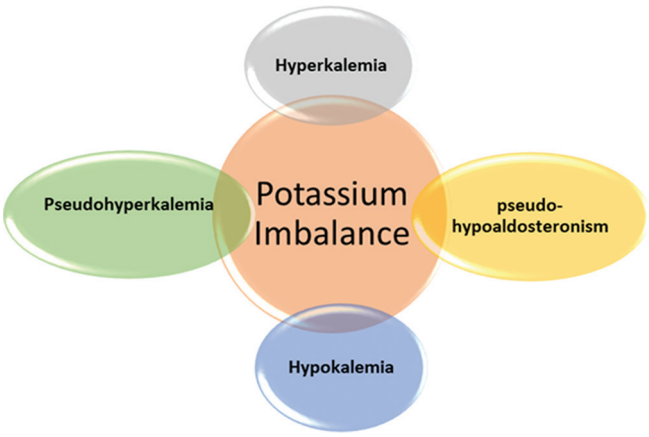

Figure 1: Major Conditions Associated with Potassium Imbalance that causes different health abnormalities and diseases

The kidney is the seat of the body's K^+ metabolism, and it maintains the body's K^+ content by controlling K^+ intake and K^+ excretion/loss. Figure 2 shows the factors that affect renal potassium excretion. Some of the important factors regulating K^+ movement across the cell under normal conditions are insulin and catecholamines.[18] Insulin, catecholamines, aldosterone, and alkalemia force potassium into the cells while increase in osmolality and acidemia shift potassium out of the cell.[12] The kidney moderates the activities of aldosterone which when over produced facilitates K^+ loss. Under normal conditions, intracellular K^+ buffers the effect of a fall in extracellular K^+ concentrations by moving into the extracellular space, but the overproduction of aldosterone affects this balance and causes continued loss of K^+.[19] Another organ involved in K^+ homeostasis is the colon. The colon is the major site of gut regulation of potassium excretion. Potassium excretion through the colon is minimal during normal conditions, but its role increases as the renal function worsens as seen in renal insufficiency or during acute potassium overload when the kidneys are overwhelmed.[12,20]

Skeletal muscle is also implicated in extracellular K^+ concentration regulation. This was demonstrated by studies in rats using a K^+ clamp technique. According to the report, there was a decrease in muscle sodium pump pool size due to K^+ deprivation. In addition, glucocorticoid treatment-induced increase in muscle Na^+-K^+-ATPase alpha2 levels. Furthermore, the body can adapt to changes in renal and extrarenal K^+ balance without significantly altering plasma K^+ level.[21] The Na^+-K^+-ATPase mechanism is still under investigation. However, there is evidence that insulin may influence the activity and expression of muscle Na^+-K^+-ATPase. Insulin forces K^+ into the cells. Insulin apart from regulating glucose metabolism after a meal also shift dietary K^+ into cells until the kidney excretes the K^+ load to re-establish K^+ homeostasis.[22-24] The ability of skeletal muscle to buffer declines in extracellular K^+ concentrations by donating some components of its intracellular stores.[25]

There are also genes involved in K^+ homeostasis, especially with-no-lysine K (WNK) genes which act at the distal convoluted tubule (DCT). The WNK genes act as molecular switches and activate the thiazide-sensitive NaCl cotransporter (NCC). Low intracellular chloride level triggers the activation of NCC by WNK kinases resulting in reabsorption of potassium at the DCT and preventing loss of potassium.[26] Mutations of the WNK1 and WNK4 genes have been observed in some patients with hyperkalemia and hypertension caused by pseudohypoaldosteronism type II (PHA2).[27]

Potassium Imbalance, Oxidative Stress and Disease

Oxidative stress (OS) is known to adversely affect health outcomes in humans. It influences the activities of inflammatory mediators and other cellular processes involved in the initiation, promotion, and progression of human neoplasms

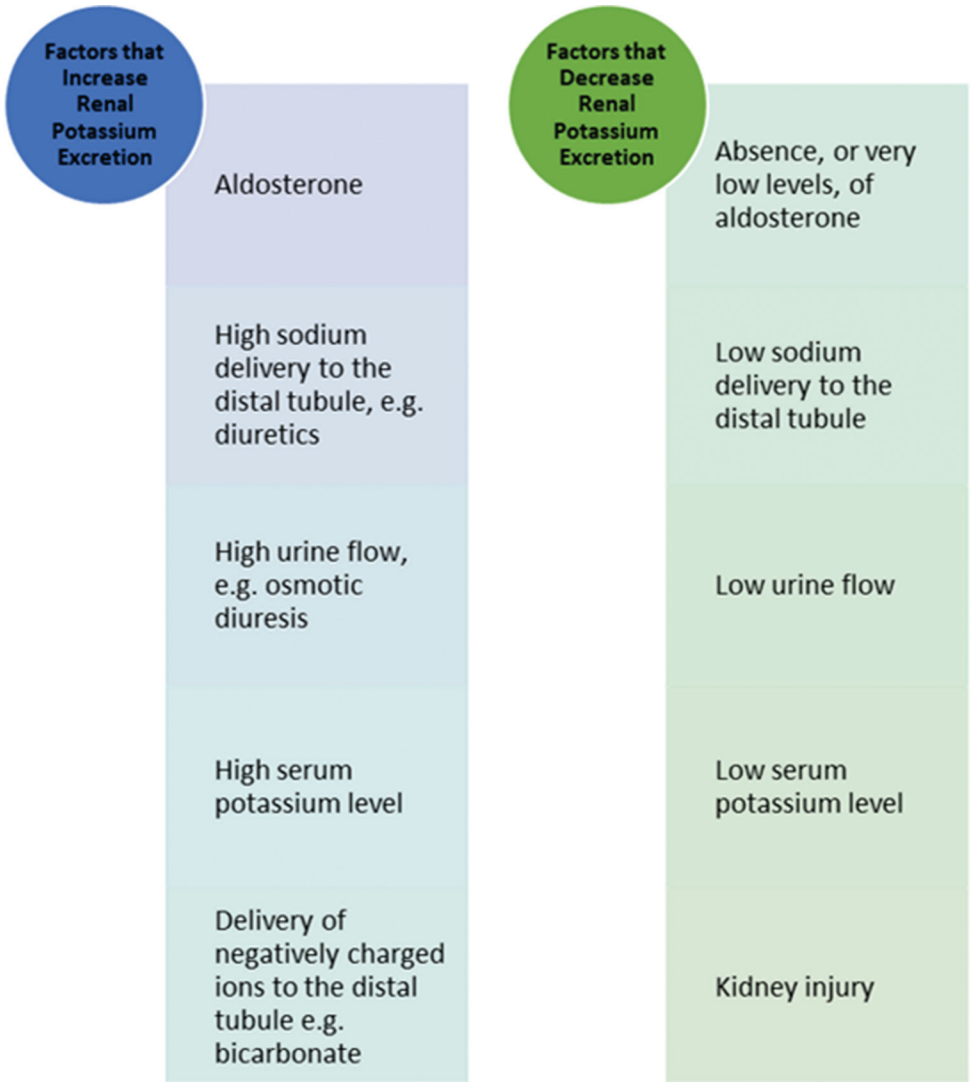

Figure 2: Factors Affecting Renal Potassium Excretion. Potassium intake, intracellular potassium concentration, distal delivery of sodium, urine flow rate, mineralocorticoid activity, and tubular responsiveness to mineralocorticoid affect renal potassium excretion

and pathogenesis of neurodegenerative diseases such as Alzheimer's disease, Huntington's disease, Lou Gehrig's disease, multiple sclerosis, and Parkinson's disease, as well as atherosclerosis, autism, cancer, heart failure, and myocardial infarction.[28,29] Likewise, abnormalities in potassium channel have been reported in neurodegenerative diseases including amyotrophic lateral sclerosis, a lethal neurodegenerative disease commonly called Lou Gehrig's disease,[30] and Parkinson's disease such that potassium channel blockers are part of the treatment regimen in Parkinson's disease.[31] Enzymes that are involved in OS also affect potassium activities. An example is heme oxygenase-1 (HO-1) whose expression is increased in the central nervous system following an ischemic insult. HO-1 is active in cancer cells and is suggested to also increase expression of HO-1. It can also can induce apoptosis by regulating K(+) channels, especially regulation of Kv2.1.[32] Koong *et al*.[33] studied how free radicals produced after exposure to hypoxia and reoxygenation activate voltage-dependent K^+ ion channels in tumor cells *in vitro*. They reported that potassium (K+) channels are activated following reoxygenation suggesting that the activation of K^+ currents is one of the early responses to OS.[33]

Sources of potassium

Potassium-rich foods include meats (pork), fish (rockfish, cod, and tuna), milk, yogurt, beans (soybeans, lima beans, and kidney beans), tomatoes, potatoes, spinach, carrot, and fruits (bananas, beet green, prune juice, peaches, oranges, cantaloupe, honeydew melon, and winter squash).[34] Ingestion of K^+ rich diets influences plasma concentration of potassium.[6] Increased potassium intake can occur through intravenous (IV) or oral potassium supplementation. Another potential but very rare source is hemolysis from packed red blood cells transfusion.[35] Enteric solute sensors are said to modulate the activities of dietary Na^+, K^+, and phosphate. After meal, the enteric sensors detect these ions and send signals to the kidney to buffer the effect through ion excretion or reabsorption. Through this mechanism, the enteric sensors may enhance

the clearance of the K^+ from diet or infusion.[36-38] A study has also suggested that dietary K^+ intake through a splanchnic sensing mechanism can signal increases in renal K^+ excretion independent of changes in plasma K^+ concentration or aldosterone.[20]

Aldosterone and potassium balance

Aldosterone, a mineralocorticoid hormone is known to moderate the body's electrolyte balance including potassium.[10] It is involved in the response to two opposite physiological conditions (aldosterone paradox): hypovolemia and hyperkalemia. One of its key mechanisms is the stimulation of Na^+ reabsorption and K^+ secretion in the aldosterone-sensitive distal nephron (ASDN).[39] Aldosterone acts by increasing the number of open sodium channels in the luminal membrane of the principal cells in the cortical collecting tubule, leading to increased sodium reabsorption hyperkalemia.[40] Aldosterone and renin-angiotensin system work together under hypovolemic condition. Low volume triggers the activation of the renin-angiotensin system which induces increased aldosterone secretion.[41] The increase in circulating aldosterone stimulates renal Na^+ retention that facilitates the restoration of ECF volume without affecting renal K^+ secretion. However, during hyperkalemia, aldosterone release is mediated by a direct effect of K^+ on cells in the zona glomerulosa. The increase in circulating aldosterone stimulates renal K^+ secretion which restores the serum K^+ concentration to normal without affecting renal Na^+ retention.[6,10]

Understanding aldosterone paradox is a complex process and it is important for the kidney to differentiate between the two opposite conditions for effective response. Angiotensin II is suggested as the key sensor of the difference between volume depletion and hyperkalemia. This is because activation of the renin-angiotensin-aldosterone system (RAAS) controls volume depletion and angiotensin II is not affected by plasma K^+ concentration.[18] In addition, renal K^+ secretion and Na^+ retention remain stable under normal condition but under pathophysiologic conditions, there is increase in distal Na^+ and water delivery coupled to increased aldosterone levels which results in renal K^+ wasting.[18] A recent study suggests that a blockade of renin-angiotensin-aldosterone activity may adversely affect extrarenal/transcellular potassium disposition as well as cause a reduction in potassium excretion in humans with renal impairment. Reduced aldosterone production impairs the responsiveness of the renal system and potassium metabolism.[42,43] Aldosterone is a drug target for certain human diseases. For example, reducing plasma aldosterone level has shown promise in reducing the risks associated with cardiovascular and renal problems in hypertensive humans but can produce hyperkalemia.[42] An emerging study is

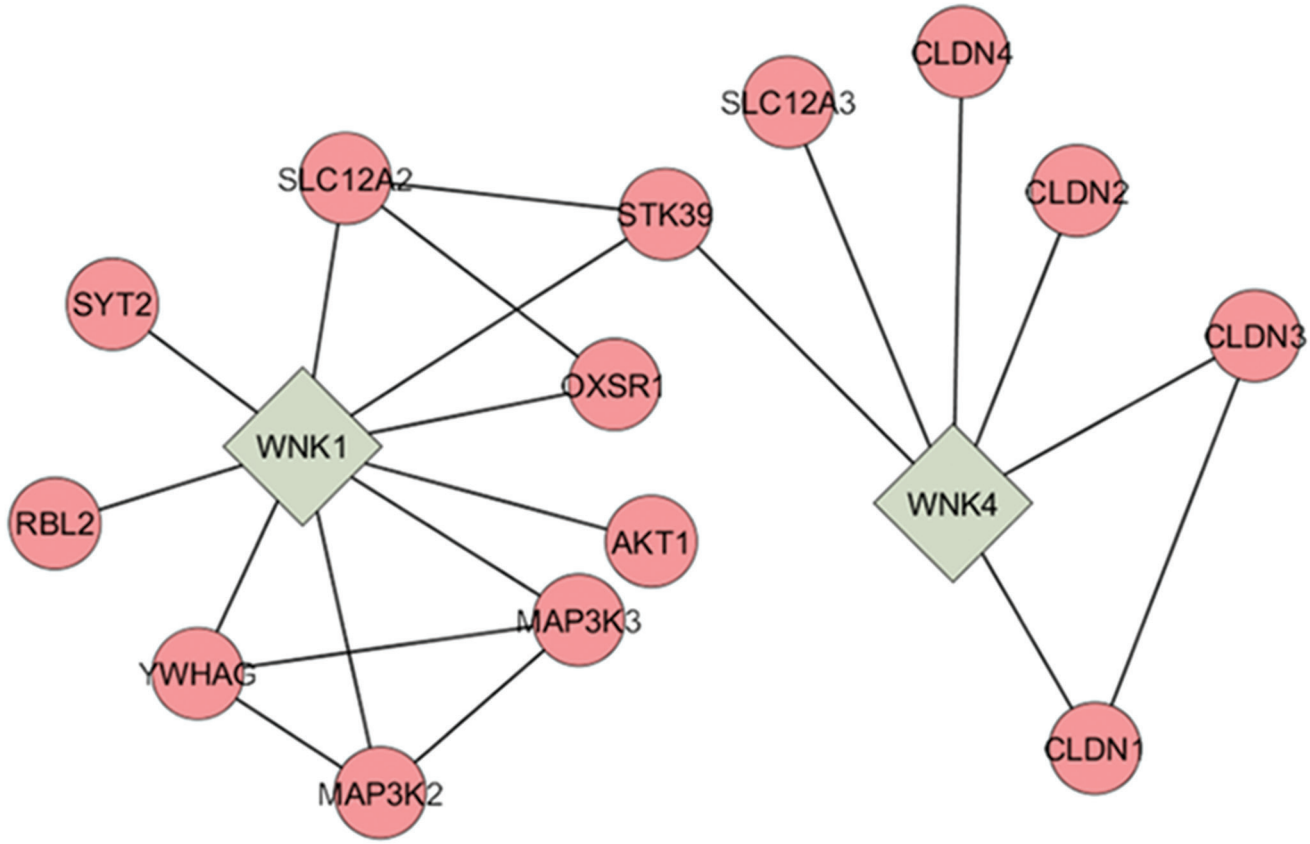

Figure 3: Molecular Interactions of Potassium Responsive Genes/Proteins: With-no-lysine K 4 has shown interaction with claudin group of proteins and other proteins known to be involved in forming a physical barrier around cell to prevent solutes and water from passing freely through the paracellular space. Image created with MiMI plugin for Cytoscape

suggesting that microRNAs may be involved in the modulation of RAAS that triggers cardiovascular inflammation seen in potassium imbalance.[44]

Vasopressin and potassium balance

Vasopressin is an important hormone that affects renal K^+ balance. Vasopressin stabilizes renal K^+ secretion during changes in flow rate.[45] Arginine vasopressin can induce an increase of low-conductance K^+ channel activity of principal cells in rat cortical collecting duct (CCD) by the stimulating cAMP-dependent protein kinase. An increase of low-conductance K^+ channel activity may lead to hormone-induced K^+ secretion in a rat CCD. A combination of endogenous vasopressin suppression and decreased distal K^+ secretion can prevent excessive K^+ loss under full hydration and water diuresis.[46]

Gene regulation of potassium homeostasis

The activities of some genes have been identified to regulate potassium homeostasis. Notable among the genes are mammalian WNK kinases which constitute a family of four serine-threonine protein kinases, WNK1-4. Mutations of WNK1 and WNK4 in human cause PHA2, an autosomal-dominant Mendelian disease characterized by hypertension and hyperkalemia.[47] WNK proteins act as molecular switches with discrete functional states that have different effects on downstream ion channels, transporters, and the paracellular pathway. Mutations in the gene encoding the kinase WNK4 can cause pseudohypoaldosteronism type II (PHAII). PHAII also called Gordon syndrome is a rare syndrome featuring hypertension and hyperkalemic metabolic acidosis. Wnk4 is a molecular switch that regulates the balance between NaCl reabsorption and K^+ secretion by altering the mass and function of the DCT through its effect on NCC.[48] Further explanation of aldosterone paradox has been made by the implication of the activity of the WNK4 in the distal nephron. These effects enable the distal nephron to allow either maximal NaCl reabsorption or maximal K^+ secretion in response to hypovolemia or hyperkalemia, respectively.[49] WNK4 has shown interaction with claudin group of proteins (claudin 1 (CLDN1), claudin 2 (CLDN2), claudin 3 (CLDN3), and claudin 4 (CLDN4). This interaction network is illustrated in Figure 3.

Claudins are tight junction proteins involved in forming a physical barrier around cell to prevent solutes and water from passing freely through the paracellular space.[50,51] CLDN2 forms a cation-selective pore in tight junctions while CLDN4 restricts the passage of cations through epithelial tight junctions. Claudins 1, 3, and 4 may be involved in separating the potassium-rich endolymph from the sodium-rich intrastrial fluid.[52] Other genes that network with WNK4 are SLC12A3 solute carrier family 12 (sodium/chloride transporter), member 3. SLC12A3 contributes in maintaining electrolyte homeostasis by encoding a renal thiazide-sensitive sodium-chloride cotransporter which mediates sodium and chloride reabsorption in the DCT. Mutations in this gene cause Gitelman syndrome (GS). Chloride channel, voltage-sensitive Kb (CLCNKB) gene is another gene that is involved in potassium homeostasis. The CLCNKB is expressed predominantly in the kidney and may be important for renal salt reabsorption. A mutation in CLCNKB results in hypokalemia as seen in autosomal recessive Bartter syndrome type 3 (BS3).[53-55] Aldosterone also stimulates the expression of the serum and glucocorticoid-inducible kinase 1, which enhances the abundance of the epithelial sodium channel, activates basolateral Na^+/K^+-ATPase activity.[39,56] This increases the electrochemical driving force for sodium reabsorption and K^+ excretion[57] necessary for potassium homeostasis regulation.

Tubular flow and potassium homeostasis

The urinary system is the major site of potassium homeostasis regulation, and under normal physiological conditions, about 90% of potassium is excreted through the urine while the remaining 10% or less is excreted through sweat, vomit, or stool.[58,59] There are differences at the rate at which potassium is secreted or excreted as the urine travels along the renal tubule. Most potassium excretion occurs in the principal cells of the CCD.[58] The late DCT, the connecting tubule, and the CCD are the segments primarily involved in renal K^+ secretion and they are collectively called the ASDN. This is because basal K^+ secretion in these segments involves the renal outer medullary K^+ channel (ROMK) whose activity and abundance is influenced by aldosterone. Potassium/sodium pump determines where, when and the amount of potassium to be excreted. That is why luminal sodium delivery to the DCT and the CCD control urinary potassium excretion. Aldosterone and other adrenal corticosteroids with mineralocorticoid activity affect the rate of potassium secretion.[60] The rates of Na^+ reabsorption as well as K^+ secretion can be related to tubular flow rates. Sodium reabsorption through epithelial sodium channels (ENaC) located on the apical membrane of cortical collecting tubule cells is driven by aldosterone and generates a negative electrical potential in the tubular lumen, driving the secretion of potassium at this site through the ROMK channels.[61] An increase in tubular flow rates can directly affect the activity of apical membrane Na^+ channels and indirectly activate a class of K^+ channels, referred to as maxi-K, which under low flow states are functionally inactive. This suggests that an increase in glomerular filtration rate (GFR) after a protein-rich meal would lead to an increase in distal flow activating the ENaC, increasing intracellular Ca^{2+} concentration, and activating maxi-K^+ channels. The body uses this process to guide against development of hyperkalemia as more K^+ are secreted and eliminated.[62] Renal potassium excretion can also be affected by some medications such as potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, and RAAS inhibitors.[63-66]

Circadian rhythm and potassium homeostasis

Like most body's physiologic processes, K^+ secretion/excretion is regulated by circadian rhythm. The rate of urinary K^+ excretion changes during a 24-h period and this may be due to changes in activity and fluctuations in K^+ intake caused

by the spacing of meals. The circadian rhythm effect is used to explain why K^+ excretion is lower at night and in the early morning hours and then increases in the afternoon in situations when K^+ intake and activity are evenly spread over a 24-h period. The kidney is the principal organ responsible for the regulation of the composition and volume of ECFs. Several major parameters of kidney function, including renal plasma flow, GFR, and tubular reabsorption and secretion have been shown to exhibit strong circadian oscillations. Renal circadian mechanisms contribute in maintaining homeostasis of water, and three major ions (Na^+, K^+, and Cl^-) and dysregulation of the renal circadian rhythms may lead to the development of hypertension and accelerated the progression of chronic kidney disease (CKD) and cardiovascular disease in humans.[67-70]

Potassium balance and myocardial activity

Potassium is very important for regulating the normal electrical activity of the heart. A shift in potassium balance will adversely affect the heart.[71] Hypokalemia may result in myocardial hyperexcitability which may lead to reentrant arrhythmias. Conversely, increase in extracellular potassium reduces myocardial excitability Electrocardiogram (EKG or ECG) taken in hypokalemic state shows increased amplitude and width of the *P* wave, prolongation of the PR interval, T-wave flattening and inversion, ST depression, prominent U waves, and an obvious long QT interval because of fusion of the T and U waves.[72] In addition, supraventricular and ventricular ectopics, supraventricular tachyarrhythmia, and life-threatening ventricular arrhythmias and Torsades de Pointes develop as hypokalemic condition persists.[73] Hypokalemia is often associated with hypomagnesemia, which increases the risk of malignant ventricular arrhythmias.[74] On the other hand, persistent hyperkalemia suppresses impulse generation leading to bradycardia and conduction blocks and eventually cardiac arrest.[75] However, serum potassium level does not always correlate with the ECG changes. Thus, patients with relatively normal ECGs may still experience sudden hyperkalemic cardiac arrest.[76] In addition, hypo/hyperkalemia can cause cardiac arrest in children.[77]

Hypokalemia

Abnormal low blood potassium level of <3.5 mEq/L is referred to as hypokalemia and it is a common electrolyte disorder in clinical practice.[14] Hypokalemia can result from inadequate potassium intake, excessive loss of potassium, and transcellular shift of potassium which is an abrupt movement of potassium from the ECF into ICF in the cells. Often hypokalemic condition is caused by drugs prescribed by physicians or due to inadequate intake. Abnormal losses can occur through renal system induced by metabolic alkalosis or loss in the stool induced by diarrhea. Metabolic alkalosis is always associated with hypokalemia and it is a salt-sensitive disorder in which there is selective chloride depletion resulting from vomiting or nasogastric drainage. Chloride-induced alkalosis can be corrected by the administration of chloride, and this allows the body to replenish its potassium store if potassium intake is insufficient. Overproduction of aldosterone (hyperaldosteronism) also causes metabolic alkalosis related severe hypokalemia (serum potassium, <3.0 mEq/L). There is a relationship between Cushin's syndrome and hypokalemia.[14] Metabolic acidosis, especially type I or classic distal renal tubular acidosis associated with hypokalemia. Interestingly, the severity of this condition is determined by the dietary sodium and potassium intake and serum aldosterone concentrations instead of the degree of acidosis. Untreated distal renal tubular acidosis could lead to a life-threatening hypokalemic

Table 1: Factors that decrease plasma potassium (Hypokalemia)

Factor	Mechanism	Reference (PMID)§
Aldosterone	Increases sodium resorption, and increases K^+ secretion/excretion	25715092,15590995
Insulin	Stimulates K^+ entry into cells by increasing sodium efflux (energy-dependent process)	2540370
Magnesium depletion	intracellular potassium concentration loss leading to renal potassium wasting	2255809
Beta-adrenergic agents	Increases skeletal muscle uptake of K^+	2540370
Alkalosis (increased pH)	Enhances cellular K^+ uptake	25856925, 25709976
b_2-Sympathomimetic Drugs e.g., albuterol	Initial dose reduces serum potassium by 0.2 to 0.4 mEq/L	24094256, 15494380
Diuretics (thiazide and loop diuretics)	block chloride-associated sodium reabsorption	9700180
Furosemide/bumetanide with metolazone	Diuretic	2384955
Acetazolamide	Impedes hydrogen-linked sodium reabsorption causing both hypokalemia/ metabolic acidosis	8977803
Genetic abnormalities		10959445
Liddle's syndrome and 11b-hydroxysteroid dehydrogenase deficiency	Stimulate reabsorption of sodium by collecting duct cells leading to mineralocorticoid excess	10959445
Bartter's syndrome	genetic mutations inactivate or impede the activity of chloride-associated sodium transporters in the loop of Henle	10959445
Gitelman's syndrome	genetic mutations inactivate or impede the activity of chloride-associated sodium transporters in early distal tubule	10959445

PMID§: Pubmed Identifier. Hypokalemia is caused by inadequate potassium intake, excessive loss of potassium, and transcellular shift of potassium. The Table describes the factors that contribute to hypokalemia, their mechanisms of action and the sources of information

level (serum potassium, <2.0 mEq/L). As mentioned earlier hypokalemia can result from extrarenal potassium loss as seen in colonic pseudo-obstruction (Ogilvie's syndrome).[78] The factors that decrease plasma potassium level are shown in Table 1.

Differential diagnosis for hypokalemia

In the diagnosis of hypokalemia, it is important to differentiate true potassium depletion from pseudohypokalemia which may be transient and arise from sampling errors, for instance, if a blood sample is taken upstream of an infusion of saline, dextrose, or other fluids that have little or no potassium. Sampling error may be confirmed from other hematological tests that will demonstrate that the collected sample is a mixture of blood and infused fluid. Some of the important tests for hypokalemia differential diagnosis include measurement of blood magnesium, aldosterone and renin levels, diuretic screen in urine, response to spironolactone and amiloride, measurement of plasma cortisol level and the urinary cortisol-cortisone ratio, and genetic testing.[5,79] Test parameters that are considered in differential diagnosis of chronic hypokalemia include blood pressure, acid-base equilibrium, serum calcium concentration, 24-h urine potassium and calcium excretion.[80,81] Hypomagnesemia can lead to increased urinary potassium losses and hypokalemia.[79,82] Urine potassium is measured to determine the pathophysiologic mechanism of hypokalemia such as the rate of urinary potassium excretion. Urine electrolyte determination may be assessed by determining the ratio of urine potassium to urine creatinine.[14]

Hypokalemia can co-exist with other diseases and can be a symptom of other diseases. For example, hyperthyroidism, familial, or sporadic periodic paralysis are considered when hypokalemia occurs with paralysis.[83] Figure 4 shows the factors considered in the differential diagnosis of hypokalemia. Determination of the acid–base balance, the blood pressure and urine excretion rate are helpful when making the diagnosis of hypokalemia of unknown cause. A common test performed is the urine potassium-creatinine ratio (K/C). Poor potassium intake, gastrointestinal losses, and a shift of potassium into cells are suspected if K/C ratio is <1.5. Barter syndrome, GS, and diuretic use are suspected if K/C ratio is >1.5 but with metabolic alkalosis and normal blood pressure. Metabolic acidosis with K/C ratio of >1.5 is associated with diabetic ketoacidosis or type 1 or type 2 distal renal tubular acidosis. In addition, metabolic alkalosis with a high urine K/C ratio and hypertension have been seen in patients with hyperaldosteronism, Cushing syndrome, congenital adrenal hyperplasia, renal artery stenosis, mineralocorticoid excess.[79] GS and BS are some of the diseases closely associated with hyperkalemia.

Gitelman syndrome

GS is an inherited renal tubular disorder mostly seen in childhood or early adulthood and it is known to be caused by a mutation in SLC12A3 gene which is a thiazide-sensitive NCC.[53] Hypokalemia is one of its classical symptoms and it may account for ~50% of all chronic hypokalemia cases.[84] Other signs include hypotension, metabolic alkalosis, hypocalciuria and hypomagnesemia and hypertrophy of the juxtaglomerular

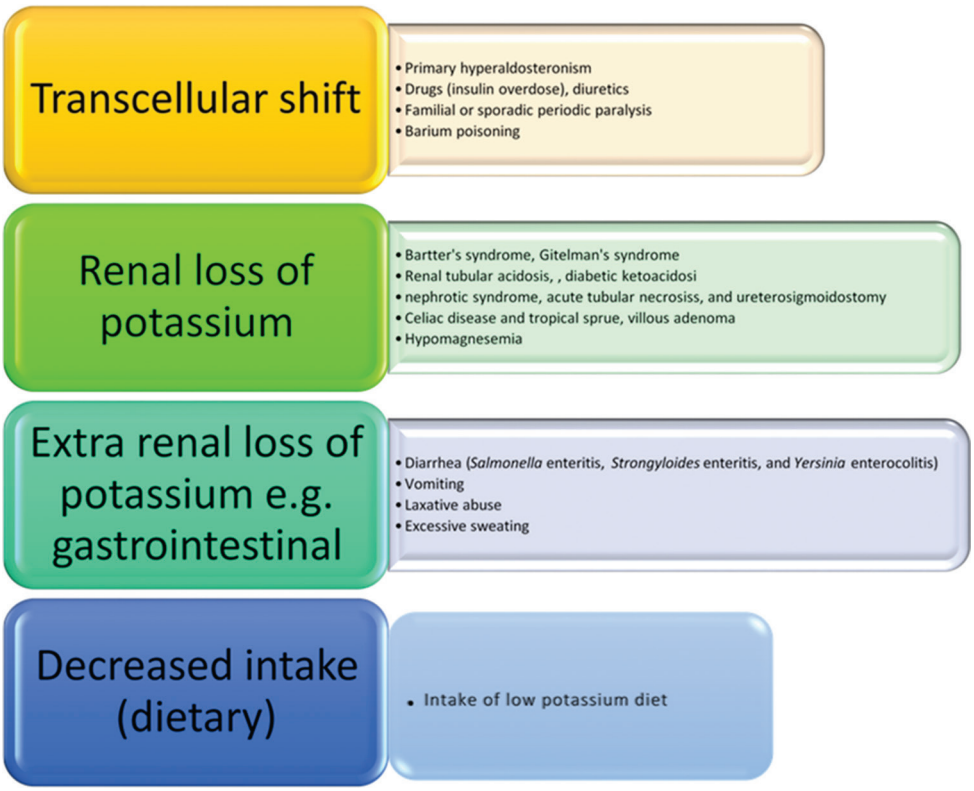

Figure 4: Differential Diagnosis of Hypokalemia Based on Types and Causes of Potassium Imbalance

complex with secondary hyperaldosteronism.[15,85] Hypokalemia is often within the range 2.4–3.2 mmol/l and patients may have low blood pressure and complaints of tiredness and increased fatigability. Patients often misdiagnosed of Bartter's syndrome and futile attempts to treat with indomethacin.[86] GS can be confirmed through genetic diagnosis by sequence analysis of the SLC12A3 gene to observe if there is a compound heterozygous mutation encoding the thiazide-sensitive sodium chloride cotransporter.[87]

Bartter syndrome

BS is like GS characterized by hypokalemic alkalosis, hypomagnesemia but with hyperreninemic hyperaldosteronemia and normal blood pressure. BS also affects infants or early childhood. Genetic analysis shows mutation in chloride channel, voltage-sensitive Kb (CLCNKB) gene.[53,55] Both BS and GS can be treated with potassium and magnesium oral supplements, for example, ramipril and spironolactone.[88]

Hyperkalemia

Hyperkalemia is defined as a serum potassium >5.5 mEq/L, the normal range is 3.5–5.5 mEq/L for adults.[5] The range is age dependent and upper limit for young or premature infants, could be up to 6.5 mEq/L. Since the kidneys are the major organs involved in potassium metabolism, any impairment of the kidneys that affects their ability to remove potassium from the blood will lead to hyperkalemia. The condition could be transient (pseudohyperkalemia), for instance, large intake of potassium from diet or infusion.[16,89] A combination of decreased renal potassium excretion and excessive potassium intake through diet or through infusion will lead to sustained hyperkalemia.[18] Prolonged fasting may induce hyperkalemia.[90] Factors that contribute to impaired renal potassium excretion include decrease in distal sodium delivery, decrease in mineralocorticoid level or activity, and abnormal collecting duct function.[12] Hyperkalemia can be an indicator that cancer patients admitted for an emergency are at high risk for developing a delirium.[91] Dysregulation in the expression of WNK genes has been linked to hyperkalemia. For example, KS-WNK1 expression is upregulated in hyperkalemia.[92,93]

Another rare but possible cause of hyperkalemia is the shift of potassium from inside the cells to the outside. This shifting of potassium can be caused by several factors such as insulin deficiency or acute acidosis. This condition produces mild-to-moderate hyperkalemia but can exacerbate hyperkalemia induced by high intake or impaired renal excretion of potassium. Hyperkalemia is also a common complication in very low birth weight infants, especially in infants with low urinary flow rates during the first few hours after birth.[94] Hyperkalemia is a serious and potentially fatal condition that can trigger a heart attack.[17] Although many individuals with hyperkalemia are asymptomatic, common symptoms are nonspecific and predominantly related to muscular or cardiac function, especially cardiac arrest.[13,95,96] Weakness and fatigue are the most common complaints. Potassium homeostasis is also critical to prevent adverse events in patients with cardiovascular disease. Studies have shown that low serum potassium levels of <3.5 mEq/L increases the risk of ventricular arrhythmias in patients with acute myocardial infarction.[97] The factors that cause hyperkalemia are shown in Table 2.

Differential diagnosis of hyperkalemia

The symptoms of hyperkalemia resemble those of other clinical diseases. An understanding of potassium physiology is helpful when approaching patients with hyperkalemia. Factors to be considered during the diagnosis of hyperkalemia are shown in Figure 5. As mentioned previously, plasma potassium concentration is influenced by potassium intake, the distribution of potassium between the cells and the ECF, and urinary potassium excretion.[12,19,61,98]

Pseudohyperkalemia could be as a result of sampling error.[17,43] Excess potassium can enter into the blood sample through

Table 2: Factors that increase plasma potassium (Hyperkalemia)

Factor	Mechanism	Reference (PMID)§
Acidosis (decreased pH)	Impairs cellular K^+ uptake	26022032, 6111930
Alpha-adrenergic agents	Impairs cellular K^+ uptake	19623566
Angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs NSAIDs, and renin-angiotensin aldosterone system (RAAS) inhibitors	Impair kidney potassium excretion	20087674, 2011243, 20030530, 20150448, 9672294, 8685062, 24804145
Cell/Muscle tissue, damage	Intracellular K^+ release, hemolysis, rhabdomyolysis	18317876
Succinylcholine	Cell membrane depolarization	25611525, 25565545, 25603385
Catecholamine	Facilitates K^+ entry into cells by stimulating cell-membrane Na+/K+ -ATPase activity	2540370
Potassium intake: diet (Potassium-rich foods e.g., meats, beans, tomatoes, potatoes, and fruits); Infusion and potassium supplements	Increase in plasma potassium level	25456880, 23855149
Packed red blood cells transfusion (PRBCs)	Hemolysis pushes K^+ from ICF to ECF	17646488
Genetic Diseases e.g., Gordon's syndrome	Increased expression of WNK1 genes	17957199,1689952,15583131
Pseudohypoaldosteronism type II (PHA2)	Mutations in WNK1 and WNK4	25904388

PMID§: Pubmed Identifier. The Table describes the factors that contribute to hyperkalemia, their mechanisms of action and the sources of information. A combination of decreased renal potassium excretion, excessive potassium intake through diet or through infusion and prolonged fasting may cause hyperkalemia

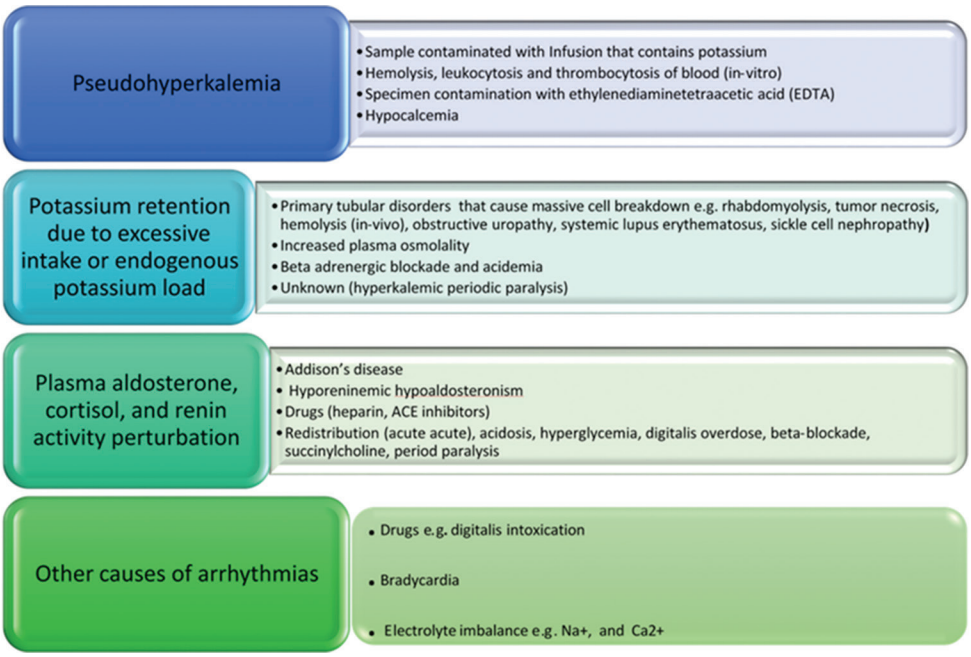

Figure 5: Differential diagnosis of hyperkalemia based on types and causes of potassium imbalance

hemolysis or ischemic muscle cells due to tight tourniquet or hand/arm exercise during the blood-drawing process. Thrombocytosis (platelet count >600,000), leukocytosis (white blood cell >200,000), or significant hemolysis (serum hemoglobin >1.5 g/dl) can cause hyperkalemia. It is advised to measure plasma potassium if thrombocytosis or severe leukocytosis is present.[5,12] Arrhythmia is a feature of hyperkalemia that could be life-threatening and that could also be caused by other diseases.[99] It is important to differentiate arrhythmia caused potassium imbalance from by other electrolyte imbalance, for example, Na^+, and $Ca2^+$ or drug for example, digitalis intoxication.[100] CKD and Gordon's syndrome are some of the diseases closely associated with hyperkalemia.

Chronic kidney disease

The main function of the kidney is to filter wastes and excess water out of the blood to be excreted as urine. The kidney is also the seat of the body's chemical balance including potassium. Kidneys adapt to acute and chronic alterations in potassium intake. When potassium intake is chronically high, the kidney is prompted to excrete more potassium. Hyperkalemia is common in patients with end-stage renal disease as in CKD.[90] In CKD patients, K^+ homeostasis appears to be well maintained until the GFR falls below 15–20 ml/min. The kidney adapts as more nephrons are lost due to CKD by making the remaining nephrons to secrete more K^+.[101] This adaptive response is similar to that which occurs due to high dietary K^+ intake in normal subjects.[102] Early stages of renal disease may not show significant abnormalities in potassium activity but renal failure hyperkalemia is a major complication in CKD patients.[103] In the presence of renal failure, the proportion of potassium excreted through the gut increases. In patients with CKD, insulin-mediated glucose uptake is impaired, but cellular K^+ uptake remains normal.[89]

Gordon's syndrome

This is a rare mineralocorticoid resistance, autosomal dominant diseases which manifests as PHA. The major features are dehydration, hypertension, severe hyperkalemia, and metabolic acidosis, but with normal GFR. Gordon's syndrome is characterized by hypertension and hyperkalemia which may be due to enhanced Na^+ reabsorption and inhibition of K^+ secretion resulting from increased WNK1 expression.[104] Intronic deletions in the WNK1 gene result in its overexpression which causes PHA2, a disease with salt-sensitive hypertension and hyperkalemia.[92] These symptoms have been attributed to overexpression of WNK1.[104] Gordon's syndrome can be treated with thiazide diuretics.[16,105]

Hypertension and potassium homeostasis

High blood pressure can be influenced by the levels of plasma potassium, low potassium causes hypertension, and increasing potassium intake lowers blood pressure.[20,106] The blood pressure of people with hypertension is lowered when they are given K^+ supplements. However, their blood pressure increases when placed on a low K^+ diet and can be worsened by increased renal Na^+ reabsorption.[98] Hypertension has been one of the symptoms of potassium-dependent diseases such as Gordon's syndrome.[105]

Conclusion

Potassium is very important in maintaining cell function such that any imbalance in K^+ will have adverse health consequences. As a result, the body has developed numerous mechanisms to make adjustment for any shift in serum K^+ homeostasis. All

the mechanisms involved are not well understood. However, much has been learned on how the body maintains a proper distribution of K^+ within the body. There is also knowledge on how the health effect of K^+ imbalance could be managed. For instance, hypokalemia can be managed by reducing potassium losses, replenishing the potassium stores, for example, oral potassium chloride administration, evaluating toxicities and treating other underlying diseases, and determining the root causes to prevent future occurrence. Hyperkalemia such as hypokalemia treatment is based on balancing the body's potassium level. In hyperkalemic condition, the strategy is to reduce the level of potassium in the blood. There are specific treatment options depending on the potassium level and the physiologic condition of the patient. Dialysis is the definitive treatment of hyperkalemia. However, IV calcium can be used to stabilize the myocardium.[107-111] Since enzymes that are involved in OS also affect potassium activities, understanding the interplay between potassium imbalance and OS will give more insight into the pathophysiology of human diseases such as cardiomyopathies, neurological syndromes, and cancer.

Financial support and sponsorship

This research was supported by a grant from the National Institutes of Health (G12MD007581) through the RCMI Center for Environmental Health at Jackson State University.

Conflicts of interest

There are no conflicts of interest.

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