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Potassium and Its Disorders

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Abstract

Potassium is the major intracellular cation in the human body. Over 98% of the total body potassium is located within the intracellular compartment. In healthy adults, the total intracellular content of potassium is equivalent to 3000–3500 mmol. Approximately 70% of this amount is found in skeletal muscle with lesser amounts in bone, red blood cells, liver and skin. The extracellular compartment contains 1–2% of the total body potassium. This uneven distribution of total body potassium is the result of an electrogenic pump, Na^+ , K^+ ATPase. This pump transports three sodium ions extracellularly in exchange of transporting two potassium ions intracellularly. This mechanism creates a ratio that determines the cell membrane potential. Maintenance of this potassium ratio and membrane potential is vital for normal nerve conduction and muscular contraction.

Keywords: hyperkalemia, hypokalemia, acidosis, alkalosis

1. Potassium physiology and homeostasis

The kidney is responsible for maintaining the total body potassium content by matching intake with excretion. Insulin and catecholamines are primarily responsible for the regulation and distribution of potassium between the intracellular and extracellular compartments [21].

Other factors that can alter the distribution of potassium between compartments include acid-base disorders, plasma osmolarity and exercise. The following section describes the effects of these factors in causing transcellular shifts of potassium.

1.1. Transcellular shifts

1.1.1. *Insulin and catecholamines*

After a meal, postprandial release of insulin shifts dietary potassium from the extracellular compartment into the intracellular compartment. This trans-cellular shift is mediated by insulin binding to cell surface receptors, which stimulates glucose uptake in insulin-responsive tissues via the glucose transporter protein, GLUT 4.

Furthermore, insulin activates the Na^+ , K^+ ATPase pump via increased intracellular CAMP production. This increases cellular uptake of potassium, thereby lowering serum potassium. In contrast to insulin, the effect of potassium regulation by catecholamines is dependent on which adrenergic receptor subtype is activated.

Activation of the beta 2 receptor triggers Na^+ , K^+ ATPase, which induces cellular potassium uptake causing a fall in serum potassium. Activation of the alpha 1 receptor has the opposite effect, causing inhibition of Na^+ , K^+ ATPase preventing cellular uptake and causing elevated serum potassium levels. These effects have important pharmacological implications. Drugs that block beta 2 receptors tend to increase serum potassium. Likewise, drugs that block the alpha 1 receptors can lower serum potassium.

1.1.2. *Aldosterone*

Aldosterone alters the distribution of potassium between the extracellular and intracellular compartments. The Na^+ , K^+ ATPase pump is activated by aldosterone and causes cellular uptake of potassium. In the absence of altered renal potassium excretion, hypokalemia can result.

Aldosterone can also increase potassium excretion via the kidneys and to some degree by the gastrointestinal tract.

Details on the actions of aldosterone in the renal tubule are further explained in Section 1.5.

1.1.3. *Hyperglycemia/hyperosmolality*

Hyperglycemia and hyperosmolality cause water movements from the intracellular to the extracellular compartment. This movement is responsible for solvent drag which transports potassium out of the cell. Additionally, cell shrinkage occurs and increases intracellular potassium concentration. There is feedback inhibition of the Na/K ATPase pump which decreases cellular uptake of potassium, thus normalising intracellular potassium. This creates a concentration gradient that allows for potassium exchange between compartments.

1.1.4. *Metabolic acidosis*

Metabolic acidosis is associated with abnormal serum potassium. Acidosis caused by inorganic anions such as NH_4Cl and HCl can result in hyperkalemia. The mechanism behind this is not understood. Organic acids such as lactic acid generally do not cause potassium shifts between compartments. Hyperkalemia may be seen in lactic acidosis; this is the result of tissue ischemia causing cellular death and release of intracellular potassium into the extracellular fluid.

1.1.5. Exercise

Exercise has multiple effects on potassium. Contraction of skeletal muscle during heavy exercise results in release of potassium. This in turn signals catecholamine release which stimulates alpha 1 adrenergic receptors to cause potassium to shift out of cells. The increase in extracellular potassium further induces arterial vasodilation in normal blood vessels, thereby increasing skeletal blood flow. Catecholamine release during exercise also activates beta 2 adrenoreceptors which increase skeletal muscle uptake of potassium, regulating potassium and minimising exercise-induced hyperkalemia.

1.2. Dietary intake

According to international dietary guidelines, the recommended dietary intake of potassium should be 90–120 mmol/day [3, 20].

Potassium is absorbed through the gastrointestinal tract and is distributed amongst the intracellular and extracellular fluid compartments. Dietary intake varies worldwide; the western diet provides 50–100 mmol of potassium daily [3, 21].

Foods that are rich in potassium include many fruits and vegetables.

After a potassium-rich meal, increases in extracellular potassium are negated by rapid cellular uptake that allows for elimination in the urine over a period of 6–8 h.

About 90% of potassium is excreted in the urine with the remaining 10% excreted via the stool.

Potassium homeostasis is controlled by the changes in renal potassium excretion. The following section describes the basic physiology of renal potassium excretion.

1.3. Renal potassium excretion

Evolving concepts in renal potassium excretion involves the recognition of reactive and predictive systems [16].

The reactive system comprises of a negative and a forward system. The negative system consists of a negative feedback loop that modulates renal potassium, on the basis of plasma potassium and serum aldosterone levels [16].

High plasma potassium concentrations or elevated serum aldosterone levels increase urinary potassium excretion bringing plasma potassium concentration back to physiologic range. The forward system describes an unidentified potassium-sensing gut factor that increases urinary potassium excretion, in response to a high potassium diet before an increase in plasma potassium concentration, or changes in plasma aldosterone levels occur [4, 5, 7]. In addition to these systems, a circadian rhythm of potassium excretion has been proposed, for instance, the predictive system which is independent of potassium intake and activity. In studies measuring urinary potassium excretion, it has been observed that urinary potassium excretion is the lowest in the night and early mornings and highest from noon to early afternoon [16].

1.4. Renal potassium handling

Serum potassium is almost completely ionised and not bound to plasma proteins. It is filtered through the glomerulus. Approximately 65–70% of potassium filtered through glomeruli is reabsorbed in the proximal tubule. Less than 10% of the filtered load reaches the distal nephron.

Potassium reabsorption in the proximal tubule primarily occurs through paracellular pathways.

Sodium reabsorption across the tubule allows for fluid absorption to occur. As a result of this process, solvent drag occurs which permits potassium reabsorption. In addition, the electrical voltage within the tubular lumen gradually becomes more positive as fluid flows down the tubule.

This change in voltage provides an additional force favouring potassium reabsorption through the paracellular pathway, which is of low resistance.

In the loop of Henle, both secretion and absorption occur. Potassium is secreted in the descending loop in deep nephrons and is reabsorbed in the ascending loop through the action of the Na^+ , K^+ 2Cl^- cotransporter. The majority of the potassium reabsorbed by this protein is recycled back into the tubular lumen by the renal outer medullary potassium channel (ROMK), an ATP-dependent apical potassium channel that transports potassium out of cells. Modest net absorption of potassium occurs as a result of this process. The site and regulation of renal potassium excretion predominantly occurs in the distal tubule and collecting duct.

The distal nephron, which comprises the distal tubule and collecting duct, has both reabsorptive and secretory functions. Potassium excretion primarily occurs here.

There are several cell types within the epithelium of the distal tubule and collecting ducts. The most important of these cell types are the principal cells, which approximate to 70% of cells and the intercalated cells. Both cell types are located within the collecting duct. Principal cells are primarily located within the cortical collecting duct and intercalated cells are dispersed throughout the entire length of the collecting duct.

Potassium secretion is by principal cells, which involves uptake of potassium from the interstitium by Na^+ , K^+ ATPase and secretion into the tubular lumen through potassium channels: ROMK and BK also known as maxi-K.

ROMK and BK are both permeable to potassium and are regulated by different mechanisms [3].

There are several factors that influence principal cells to secrete potassium. These factors include low potassium diet, high potassium diet, angiotensin II, high serum potassium, aldosterone, luminal flow rate, extracellular pH and high Na delivery.

Sodium delivery to the distal tubule is the major regulator of potassium excretion. High sodium delivery stimulates potassium secretion. It achieves this in two ways. Firstly, increased sodium delivery causes increased sodium entry via epithelial sodium channels (ENaC), which depolarises the apical membrane causing an increase in the electrochemical gradient, promoting outward flow potassium through the potassium channels. Secondly, the more sodium delivered to the tubule, the more sodium is pumped out by Na^+ , K^+ ATPase and more potassium is pumped in [3].

This potassium is then secreted across the apical membrane of principal cells into the luminal fluid by apical potassium channels.

At low dietary loads of potassium, there is no secretion by either channel. The body is conserving potassium. ROMK channels are sequestered into intracellular vesicles. BK channels are closed [3]. In normal concentrations of potassium, ROMK channels secrete potassium whereas BK channels remain closed. In conditions where there is high potassium secretion, for example, high potassium diet, both ROMK and BK channels are open [3].

Angiotensin II is an inhibitor of potassium secretion; its mode of action is to decrease activity of ROMK, thereby limiting potassium flux into the tubular lumen.

The intercalated cells are subdivided into type A which are numerous, type B which are limited in number and non-A and non-B cells.

The intercalated cells, particularly type A, reabsorb potassium. Type A intercalated cells reabsorb potassium via the H^+ , K^+ ATPase, located within the apical membrane which actively takes up potassium from the lumen in exchange for hydrogen ions. Potassium can then enter the tubular interstitium across the basolateral membrane via potassium channels. In conditions of low potassium, potassium depletion increases H^+ , K^+ ATPase expression resulting in increased active potassium reabsorption and decreased potassium excretion.

An important regulator of potassium in the distal nephron is the enzyme with no lysine kinases (WNK kinases). WNK kinases activate sodium reabsorption in the distal tubule and inhibit the ROMK channel [16, 22].

As a result of this, there is decreased sodium delivery to the collecting duct, and coupled with this is decreased ROMK expression leading to decreased potassium secretion [16, 22].

WNK kinase activity is sensitive to chloride and potassium concentrations [16, 22].

1.5. Aldosterone paradox

Aldosterone has the ability to signal the kidney to cause sodium retention without potassium secretion in states of volume depletion but can also stimulate potassium secretion without sodium retention in the hyperkalemic state [6].

In humans, aldosterone is the major mineralocorticoid. It promotes sodium absorption and potassium excretion by binding to mineralocorticoid receptors located in the distal tubules and collecting ducts. Aldosterone increases Na^+ , K^+ ATPase activity in the basolateral membrane which is responsible for sodium reabsorption across the luminal membrane. This increases the electronegativity of the lumen which increases the electrical gradient and potassium permeability.

In states of volume depletion, the renin-angiotensin-aldosterone axis is activated and causes renal sodium absorption restoring extracellular fluid volume without a demonstrable effect on renal potassium excretion. In the presence of hyperkalemia, release of aldosterone increases urinary potassium excretion, thereby restoring serum potassium levels to normal. This effect, however, does not result in sodium renal retention.

2. Disorders of potassium

2.1. Hypokalemia

2.1.1. Epidemiology

Hypokalemia is defined as serum potassium concentration levels of <3.5 mmol and is a common electrolyte disturbance amongst hospitalised patients [6].

As many as 20% of hospitalised patients are found to have hypokalemia, but only 4–5% of this is deemed to be clinically significant [6, 13, 22].

There are no significant differences in its prevalence amongst males and females [6].

2.1.2. Aetiology

2.1.2.1. Redistribution

About 2% of the total body potassium is within the extracellular compartment. Consequently, small shifts of potassium from the extracellular compartment to the intracellular compartment can cause hypokalemia. Additionally, glycogenesis during total parenteral nutrition or enteral hyperalimentation causes insulin release which shifts potassium into cells. Furthermore, the sympathetic nervous system is involved in the activation of the beta 2 receptors causing intracellular shift of potassium. Stimulation of beta 2 receptors can also occur in thyrotoxicosis.

A rare cause of redistribution-induced hypokalemia is hypokalemic periodic paralysis. In this condition, flaccid paralysis and muscular weakness occur during the night or early mornings, typically after ingestion of a large carbohydrate meal.

2.1.2.2. Renal potassium losses

Renal potassium losses are the most common cause of hypokalemia.

Drugs are common causes of renal potassium loss.

Thiazide and loop diuretics block sodium reabsorption in the distal convoluted tubule and loop of Henle, respectively. Reabsorption does not occur proximal to the collecting duct, thereby increasing sodium delivery to the principal cells of the collecting duct. This stimulates sodium uptake and at the same time promotes potassium secretion causing potassium loss resulting in hypokalemia.

High dosage of penicillins is thought to cause hypokalemia by increased sodium delivery to the collecting duct and principal cells which result in urinary potassium secretion [22].

The antifungal agent amphotericin directly increases collecting duct secretion of potassium. This is achieved by its direct action of binding to collecting duct cells and forming pores which result in potassium loss.

The mechanism of action for aminoglycosides causing hypokalemia is not completely understood [22]. It is postulated that ROMK is activated by aminoglycosides causing urinary potassium secretion [22].

Cisplatin, an antineoplastic agent can cause both hypokalemia and hypomagnesemia.

Hypokalemia is related to hypomagnesemia. Magnesium mediates inhibition of ROMK. In states that where there is magnesium deficiency, ROMK inhibition is lost enabling potassium excretion [22].

Coupled with this is inhibition of Na⁺, K⁺ ATPase pump caused by low magnesium, causing potassium to be excreted via K channels particularly in the thick ascending limb [22].

Toluene is thought to lead to potassium wasting by causing renal tubular acidosis (RTA) [22].

Licorice and herbal cough mixtures contain glycyrrhizic and glycyrrhetic acids. They are thought to exert mineralocorticoid effects leading to hypokalemia [22].

Bicarbonaturia results from metabolic alkalosis, distal RTA or treatment with proximal RTA.

Increased distal tubular bicarbonate delivery increases potassium secretion.

Magnesium deficiency can cause high potassium excretion and potassium deficiency. Under ideal conditions, intracellular magnesium inhibits the apical ROMK channel. In magnesium deficiency, the ROMK channel is not inhibited by magnesium resulting in increased potassium excretion.

Magnesium deficiency should be suspected when potassium replacement does not correct the hypokalemia.

Intrinsic renal potassium transport defects are rare. Bartter's, Gitelman's and Liddle's are such conditions. A review of these conditions is not described here.

Similarly, detailed descriptions of genetic defects that result in elevated levels of aldosterone, glucocorticoid remediable aldosteronism, congenital adrenal hyperplasia and syndrome of apparent mineralocorticoid excess, are not described in great detail here (See **Table 1**).

Drugs	Hormones	Renal tubular defects	Genetic defects
<ul style="list-style-type: none"> • Thiazide diuretics • Loop diuretics • Penicillins; Piperacillin-Tazobactam • Amphotericin B • Aminoglycosides • Cisplatin • Toluenes • Herbal cough mixtures 	<ul style="list-style-type: none"> • Aldosterone 	<ul style="list-style-type: none"> • Bartter syndrome • Gitelman syndrome • Liddle syndrome 	<ul style="list-style-type: none"> • Glucocorticoid-remediable aldosteronism • Syndrome of apparent mineralocorticoid excess • Congenital adrenal hyperplasia

Table 1. Causes of renal potassium losses.

2.1.2.3. *Extra-renal potassium losses*

The skin and gastrointestinal tract excrete small amounts of potassium. Excessive sweating or chronic diarrhoea can cause potassium losses. Likewise, vomiting or nasogastric suction can cause hypokalemia although gastric fluids contain only 5–8 mmol/l of potassium. This is associated with concomitant metabolic alkalosis and intravascular volume depletion which cause secondary hyperaldosteronism and increases urinary potassium loss.

2.1.2.4. *Pseudohypokalemia*

Pseudohypokalemia occurs when serum potassium decreases artifactually after phlebotomy.

Acute leukemia is the most common cause. Abnormal leucocytes take up potassium when blood is stored in collection vial for a prolonged period of time at room temperature. Rapid separation of plasma and storage at 4°C are used for diagnosis.

Clinical features: the clinical manifestations of hypokalemia are proportionate to the degree and duration of serum potassium reduction.

Symptoms are often not present until serum potassium is below 3.0 mmol/L.

A potentiating factor such as digoxin can predispose hypokalemic patients to have cardiac arrhythmias because of altered resting membrane potential.

2.1.2.5. *Cardiac*

Epidemiological studies have linked hypokalemia and low potassium diet with an increased prevalence of hypertension.

Potassium deficiency can increase blood pressure. Mechanisms that have been proposed to be responsible for this effect include sodium retention with subsequent increased intravascular volume and endogenous vasoconstriction which sensitises the vasculature.

Electrocardiographic (ECG) changes with cardiac arrhythmias can be seen. Common ECG changes are U waves and ST segment depression along with T wave flattening.

2.1.2.6. *Hormonal*

Hypokalemia impairs insulin release and induces insulin resistance which worsens glycemic control in diabetic patients.

2.1.2.7. *Muscular*

Hypokalemia can lead to skeletal muscle weakness and increases sensitivity to develop exertional rhabdomyolysis by reducing skeletal muscle blood flow. Furthermore, hypokalemia hyperpolarises skeletal muscle reducing muscle contraction.

2.1.2.8. Renal

Hypokalemia can lead to significant disturbances in renal function.

Reduced medullary blood flow and increased renal vascular resistance may result in hypertension, tubulointerstitial and cystic changes, acid base disturbances and damage to the renal concentrating mechanisms [22].

Potassium deficiency can cause tubulointerstitial fibrosis which is seen in the outer medulla. The duration of hypokalemia determines the degree of damage. Prolonged hypokalemia may result in renal failure. Furthermore, chronic potassium deficiency causes renal hypertrophy that can lead to renal cyst formation particularly during increased mineralocorticoid use [22].

Hypokalemia increases renal ammonia production.

Metabolic alkalosis is associated with hypokalemia and occurs because of increased renal net acid secretion as a result of increased ammonia excretion [22].

Additionally, it can also cause increased urinary potassium secretion resulting in hypokalemia.

In cases of severe hypokalemia, respiratory muscle weakness may arise leading to the development of respiratory acidosis and if severe, respiratory acidosis.

Severe potassium depletion can cause polyuria, with urinary outputs measuring 2–3 L.

Increased thirst and nephrogenic diabetes insipidus are factors potentiating the severity of polyuria. Nephrogenic diabetes insipidus is a result of decreased expression of water transporter aquaporin 2 (AQP2) and urea transporter proteins UT-A1, UT-A3, and UT-B which take part in urine concentration mechanisms and water reabsorption [22].

2.1.2.9. Nervous system

Cramps, paresthesias, paresis, and ascending paralysis are typical features of neurological involvement.

2.1.2.10. Treatment

Treatment approach is dependent on the severity of hypokalemia and the presence of symptoms. Treatment should include reducing the amount of potassium lost, replenishing potassium stores, assessing for potential toxicities, and determining the cause so that future episodes can be prevented [6, 22].

Short-term risks of hypokalemia are cardiovascular arrhythmias and neuromuscular weakness which can be life-threatening and require urgent treatment in the form of intravenous potassium usually 5–10 mmol over 15–20 min [22].

Urgent treatment for hypokalemia however is rarely required [14].

It should be noted that the body responds to potassium losses, by shifting potassium from the ICF compartment to the ECF compartment, minimising change in extra-cellular potassium. With potassium replacement, potassium is shifted back into the ICF. The degree or magnitude of potassium deficiency can be masked. The amount of potassium required to replace the potassium lost is greater than predicted change in extra-cellular volume [6, 22].

The severity of hypokalemia determines the administration of either intravenous or oral potassium. Patients presenting with potassium levels of 2.5–3.5 mmol represent mild to moderate hypokalemia and can be treated with oral potassium supplements. Severe hypokalemia defined as potassium levels of <2.5 mmol should be treated with intravenous potassium [6, 22].

Hypokalemia is associated with magnesium deficiency. Magnesium is important for potassium uptake and for maintenance of intracellular potassium levels particularly in the myocardium [1].

2.1.2.11. Intravenous potassium

Intravenous potassium infusions can cause pain if given peripherally via a small vein. The maximum rate of potassium administration peripherally is 10 mmol/h [1, 6, 22].

In cases where more rapid replacement is necessary, potassium infusion rates >10 mmol/h can be administered but require central access, electrocardiograph monitoring and frequent monitoring of serum potassium [1, 6, 22].

2.1.2.12. Oral potassium

Oral potassium supplements can take the form of potassium chloride or effervescent tablets.

Potassium chloride tablets contain 8 mmol of potassium per tablet, as opposed to effervescent tablets which contain 14 mmol per tablet (**Table 2**).

2.2. Hyperkalemia

2.2.1. Epidemiology

Hyperkalemia occurs frequently amongst patients with chronic kidney disease, diabetes and heart failure and patients using RAAS inhibitors (renin-angiotensin-aldosterone) or NSAIDS (non-steroidal anti-inflammatories). Less than 1% of normal healthy adults develop hyperkalemia [22].

2.2.2. Aetiology

Hyperkalemia can be the result of pseudohyperkalemia, potassium redistribution from intracellular fluid to extracellular fluid and imbalances between potassium intake and excretion.

Hypokalemia	Treatment
Mild (3.0–4.0 mmol)	Oral potassium: <ul style="list-style-type: none"> • Effervescent tablets 1–2 tabs bd (14–28 mmol) • Potassium chloride tablets 1–2 tabs bd (8–16 mmol) • IV potassium; 60 mmol/24 h
Moderate (2.5–3.0 mmol)	Oral requirements; total requirements are 96 mmol/day [2]. IV potassium infusion; 90 mmol/24 h [2]
Severe (<2.5 mmol)	IV potassium infusion: 5–10 mmol/h

Table 2. Treatment of hypokalemia.

In this section, a brief description of each cause is given.

2.2.3. Pseudohyperkalemia

Release of potassium from erythrocytes after phlebotomy occurs. Free hemoglobin is released into plasma from damaged erythrocytes and is reported as hemolysis. In the presence of hemolysis, reported plasma potassium is not representative of the actual plasma potassium. Treatment should not be initiated, and repeat measurement of plasma potassium must take place.

Ischemia from difficult phlebotomy or exercise of limb in the presence of tourniquet can lead to abnormally increased potassium values. Potassium can also be released from other cellular elements present in blood during clotting particularly, with severe leucocytosis ($>70,000/\text{cm}^3$) or thrombocytosis. About one-third of patients with platelet counts of $500\text{--}1000 \times 10^9$ have pseudohyperkalemia [22].

Diagnosis of pseudohyperkalemia is made by measuring serum/plasma potassium.

2.2.3.1. Redistribution

Hyperglycemia from insulin deficiency and hyperosmolarity are important causes of potassium movement from the intracellular fluid to the extracellular fluid. Moreover, medications such as beta 2 adrenoreceptor antagonists, RAAS inhibitors and mineralocorticoid receptor blockers are common agents that can cause hyperkalemia.

2.2.3.2. Potassium intake

In general, excessive dietary intake does not cause chronic hyperkalemia because the kidney can excrete ingested potassium.

There are other factors that contribute to hyperkalemia when renal potassium excretion is impaired.

2.2.3.3. *Impaired potassium excretion*

In patients with decreased kidney function, there is impaired potassium excretion.

In chronic kidney disease, renal potassium secretion from distal nephrons is preserved until the glomerular filtration rate is reduced to 10–20 ml/min [22].

Medications can affect potassium excretion. A list of medications and their effects is described in **Table 3**.

Hyperkalemia may occur in obstructive uropathy. This is in part due to decreased Na⁺, K⁺ ATPase expression and activity. It can persist for months or years after the obstruction is relieved [22].

This is thought to be due to a persistent defect in the collecting duct, where secretion is impaired. Aldosterone deficiency is not responsible.

Class	Class example	Mechanism
Potassium-containing drugs	Potassium chloride	Increased potassium intake
Beta adrenergic blockers	Propranolol, metoprolol, and atenolol	Inhibition of renin release
Angiotensin-converting enzyme (ACE) inhibitors	Ramipril, perindopril, and lisinopril	Inhibition of angiotensin I to angiotensin II
Angiotensin receptor blockers	Irbesartan, losartan, and candesartan	Inhibition of angiotensin I receptor by angiotensin II
Direct renin inhibitors	Aliskiren	Inhibition of renin activity resulting in decreased angiotensin II production
Heparin	Heparin sodium	Inhibition of aldosterone synthase, rate-limiting enzyme for aldosterone synthesis
Aldosterone receptor antagonists	Spironolactone and eplerenone	Block aldosterone receptor activation
Potassium-sparing diuretics	Amiloride and triamterene	Block collecting duct apical ENaC channel, decreasing gradient for K secretion.
NSAIDS and COX-2 inhibitors	Ibuprofen	Inhibition of prostaglandin stimulation of collecting duct potassium secretion. Inhibition of renin release
Digitalis glycosides	Inhibition of Na ⁺ , K ⁺ ATPase necessary for collecting duct K secretion and regulation of K distribution into cells.	Digoxin
Calcineurin inhibitors	Inhibition of Na ⁺ , K ⁺ ATPase necessary for collecting duct K secretion.	Cyclosporine and tacrolimus

Table 3. Pharmacological agents causing hyperkalemia. Class Example and Action description for digoxin and CNI need to be reversed, for eg action of drug for digoxin under class example and class example digoxin is under action of drug, this also applies FOR CNI.

2.3. Clinical manifestations

Hyperkalemia may be asymptomatic or cause life threatening arrhythmias.

2.3.1. Cardiac

Hyperkalemia decreases the transmembrane potassium gradient. This results in cell membrane depolarisation, slowing of ventricular conduction and decrease in the duration of the action potential. These changes result in electrocardiogram (ECG) manifestations including peaked T waves, broadening of QRS complexes, loss of p wave and ventricular fibrillation which can lead to asystole. Changes in plasma potassium may not result in ECG changes. ECG has been described to be a poor tool for detecting hyperkalemia with a sensitivity of 34–40% [9–12, 15].

2.3.2. Neuromuscular

Neuromuscular effects include paresthesias, weakness and paralysis. Deep tendon reflexes may be depressed or absent. Sensory findings are absent.

2.3.3. Gastrointestinal

Nausea, vomiting and diarrhoea can occur but are less encountered.

2.4. Diagnosis

Transtubular potassium gradient (TTKG) can help distinguish renal causes of hyperkalemia from non-renal causes.

It is a measurement of net potassium secretion by the collecting duct after correcting for changes in urinary osmolality.

The formula is as follows Eq. (1):

$$TTKG = \frac{\text{urine potassium} \cdot \text{urine osmolality}}{\text{plasma potassium} \cdot \text{plasma osmolality}} \quad (1)$$

2.4.1. Effects on the cardiac system

Calcium given by the parenteral route does not produce changes in extracellular potassium but stabilises cell membrane potential by ameliorating the effects of hyperkalemia on myocardial conduction system and depolarisation [22] (Tables 4 and 5).

Responses occur within a few minutes and duration of action is between 30 and 60 min.

Although there are no clinical studies assessing efficacy, it has been accepted for the treatment of hyperkalemia when life threatening ECG changes are present or when cardiac arrest occurs. Life-threatening ECG changes include absent P waves, broad QRS complexes and sine-wave pattern.

TTKG	Indication
<5–7	Suggest aldosterone deficiency or resistance
6–12	Normal
>10	Suggest normal aldosterone action and extra renal cause of increased potassium.

Table from Comprehensive Clinical Nephrology 6th Edition. 2019.

Table 4. Interpretation of TTKG.

Medication	Dose	Route of administration	Time of onset	Mechanism
Calcium gluconate	Calcium gluconate 10%	Intravenous	1–3 min	Cell membrane stabilisation
Calcium chloride	Calcium chloride 10 mls			
Insulin with dextrose	10 units IV with 50 mls of 50% dextrose	Intravenous	30 min	Cellular potassium uptake
Beta 2 adrenergic agonist	Salbutamol 15–20 mg	Nebuliser	30 min	Cellular potassium uptake
Sodium polystyrene sulfonate	30 g–60 g	Oral	>2 h	Potassium removal by potassium binding resins
*Sodium bicarbonate**	25–100 mls 8.4% NaHCO ₃ over 5–15 minutes	Intravenous	within 60 min	Transcellular shift by alkalinisation Bicarbonate affecting H/K exchange; pushes potassium back into cells.

*Sodium bicarbonate can be considered if acidemia is present; pH <7.2.

**Hemodialysis is the most effective method of removal of potassium. Acute hemodialysis is indicated when hyperkalemia is life threatening and is refractory to medical treatment. The more severe the hyperkalemia is, the more rapid reduction of plasma potassium is required, until serum potassium is <6.0 mmol/L.

Table 5. Treatment of hyperkalemia.

The dose of calcium gluconate is higher than calcium chloride because it requires liver metabolism to release calcium.

2.4.2. Cellular uptake of potassium

Insulin and beta 2 adrenergic agonists stimulate cellular uptake of potassium. Insulin achieves this by binding to insulin receptors located on skeletal muscle. The duration of action for insulin can last for 4–6 h. Glucose is co-administered to prevent hypoglycemia.

Beta 2 receptor adrenergic agonists can be administered via inhalation and subcutaneous or intravenous routes. Tachycardia is a significant complication of therapy particularly at high doses required to treat hyperkalemia (2–8 times higher given for bronchodilation).

It has been reported that upto 25% of patients with hyperkalemia do not respond to beta 2 agonist therapy [17, 19].

2.4.3. Potassium removal

Reducing total body potassium involves decreased oral intake, enhanced fecal and urinary potassium excretion and dialysis.

In terms of dietary intake, limited amounts of citrus fruits, potatoes, tomatoes and salt products should be ingested.

Hemodialysis is the most effective mode of removal of potassium. In patients with advanced renal failure, the ability of the distal nephron to excrete potassium is reduced. In these patients, hemodialysis is the preferred mode of removal.

Oral potassium binding resins are other agents used in the treatment of hyperkalemia.

This is best observed in patients with chronic hyperkalemia. Sodium polystyrene sulfonate and calcium polystyrene sulfonate are common agents used. They exchange sodium and calcium, respectively, for potassium in the gastrointestinal tract. It can be administered orally or rectally as a retention enema. Furthermore, polystyrene sulfonates have been reported to cause constipation, intestinal necrosis and colonic perforation. Consequently, newer agents have been developed and are being evaluated in clinic trials.

Sodium zirconium cyclosilicate (ZS-9) is an oral cation exchanger designed to trap monovalent cations in the gastrointestinal tract. Its framework structure is full of micropores that allow selectivity of trapping potassium ions in exchange for sodium and hydrogen. Clinical trials have demonstrated its success in lowering plasma potassium levels within 24 h. The onset of action is 1 h following the first dose. Dose has varied from 2.5 to 10 g. Dose-dependent oedema is a notable side effect. It should be given 2 h apart from oral medications with gastric pH dependence. It binds potassium throughout the gastrointestinal tract. The bioavailability is 7 h after the onset of action after the first dose. Location of potassium binding is predominantly in the distal colon.

Long-term effects on mortality are still yet to be confirmed. In May 2018, the FDA approved ZS-9 for the treatment of hyperkalemia. It is known as Lokelma in the USA.

Patiromer is another new agent that binds potassium in the lumen of the gastrointestinal tract.

It consists of a polymer anion (the active moiety patiromer) and a calcium-sorbitol complex.

Clinical trials have shown a reduction in plasma potassium levels but there are some side effects that have been observed. Hypomagnesemia has been reported in patients taking this agent.

Its use in patients with cardiac arrhythmia has been questioned, as hypomagnesemia can be associated with cardiac arrhythmias. It can also cause gastrointestinal side effects, for example, mild to moderate constipation. Its brand name is Veltessa.

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