WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 7, 368-386. Review Article ISSN 2277–7105

HYPERKALEMIA: A COMPREHENSIVE REVIEW OF MECHANISMS, RISK FACTORS, AND MANAGEMENT APPROACHES

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Article Received on 28 Feb. 2026,
Article Revised on 18 March 2026,
Article Published on 01 April 2026,

https://doi.org/10.5281/zenodo.19326542

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How to cite this Article: Mr. Sujit S. Karande*, Ms. Rajnandini C. Koshti, Mr. Ayush A. Shendage, Mr. Shriram G. Kumbhar, Ms. Swati S. Dabhole, Ms. Aditi S. Haval. (2026). Hyperkalemia: A Comprehensive Review of Mechanisms, Risk Factors, And Management Approaches. World Journal of Pharmaceutical Research, 15(7), 368–382.

ABSTRACT

A clinically relevant disorder that can result in potentially fatal heart consequences is hyperkalemia. Patients with chronic kidney illness, kidney transplant recipients, and those using drugs that upset potassium homeostasis are frequently affected. Hormonal imbalances, transcellular potassium changes, and reduced renal potassium excretion are the causes of the illness. A significant contributing factor is drug-induced hyperkalemia, especially with calcineurin inhibitors, RAAS inhibitors, potassium-sparing diuretics, and treatments including trimethoprim. To avoid major consequences, early detection and proper treatment are crucial. This includes stabilizing cardiac membranes, redistributing potassium, and eliminating excess potassium.

KEYWORDS: Hyperkalemia; Drug-induced hyperkalemia; Chronic kidney disease; Kidney transplantation; Potassium homeostasis; RAAS inhibitors; Management.

INTRODUCTION

A serum potassium content of more than 5.0 mEq/L is known as hyperkalemia, a frequent and possibly fatal electrolyte imbalance. Since the intracellular compartment contains around 98% of the body's potassium, potassium homeostasis is strictly regulated. As a result, even slight changes in the extracellular potassium concentration can have a substantial impact on cardiac conduction and neuromuscular function.[1] If severe hyperkalemia is not identified

and treated right once, it can cause rapid cardiac death, conduction problems, muscle weakness, and potentially fatal arrhythmias.[2]

Hyperkalemia is most common in hospitalized patients and those with underlying renal or cardiovascular conditions. The primary pathogenic mechanism in patients with chronic kidney disease (CKD) is decreased renal potassium excretion, and the risk gradually rises as glomerular filtration rate falls.[3] Additionally, renin-angiotensin-aldosterone system inhibitors (RAASi), which are both cardioprotective and nonprotective, decrease aldosterone-mediated potassium excretion and hence put vulnerable people at risk for potassium retention, often result in hyperkalemia.[4] The combined consequences of diminished graft function, pre-existing chronic kidney disease (CKD), diabetes mellitus, hypertension, and exposure to several drugs that interfere with renal potassium management make kidney transplant recipients an especially vulnerable group. In this context, drug-induced hyperkalemia is especially common. Tacrolimus and cyclosporine are examples of calcineurin inhibitors that reduce distal tubular potassium output and may cause functional aldosterone resistance.[5] Trimethoprim, which is frequently used for the prevention of Pneumocystis jirovecii, also helps by lowering potassium excretion by inhibiting the distal nephron's epithelial sodium channels. Furthermore, the risk of persistent hyperkalemia is increased by concurrent use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.[6]

Serum potassium levels can be abruptly raised by transcellular potassium shifts brought on by insulin insufficiency, metabolic acidosis, hyperglycaemia, or tissue degradation in addition to impeded excretion.[7] Increased dietary consumption may worsen potassium retention in patients with impaired kidney function, even though it seldom results in hyperkalemia in people with normal renal function. Thus, hyperkalemia often has a complex origin, especially in patients with post-transplant status or advanced chronic kidney disease.[8]

Hyperkalemia is a major clinical problem because of its substantial correlation with cardiovascular morbidity, death, and the cessation of disease-modifying treatments. Early detection of triggering variables, sensible adjustments to contributing drugs, dietary counselling, and prompt pharmacologic intervention are all necessary for management. By reducing the danger of hyperkalemia and enabling the continuance of RAAS blocking, recent developments in potassium-binding drugs have increased treatment choices for chronic management.[9]

The goal of this review is to present a thorough analysis of the epidemiology, pathophysiology, risk factors, and current management approaches for hyperkalemia, with a focus on drug-induced processes and high-risk groups such kidney transplant recipients and patients with chronic kidney disease.[10]

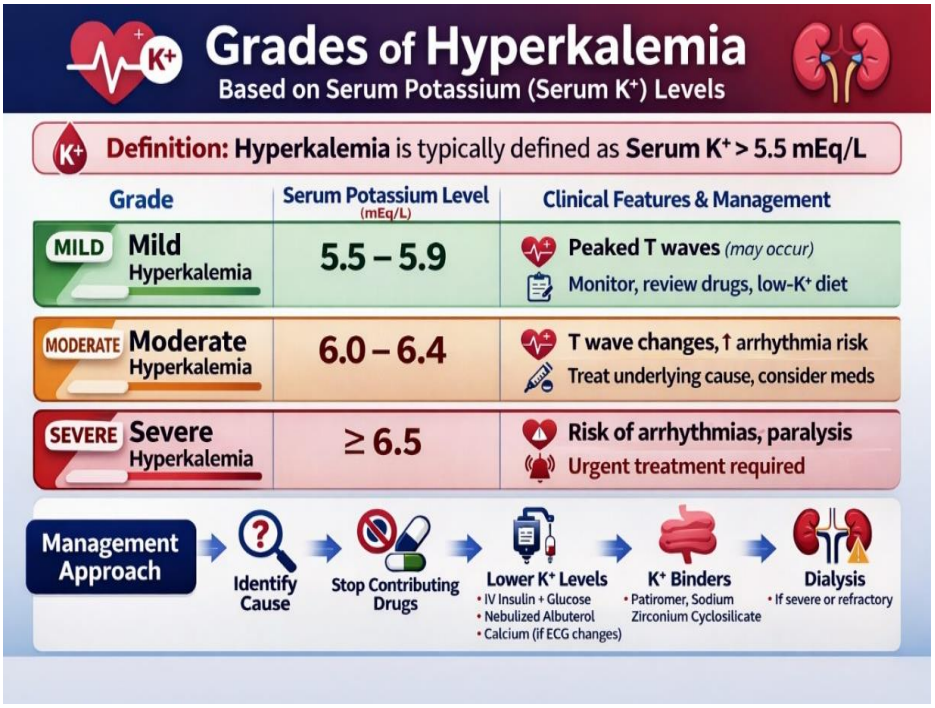
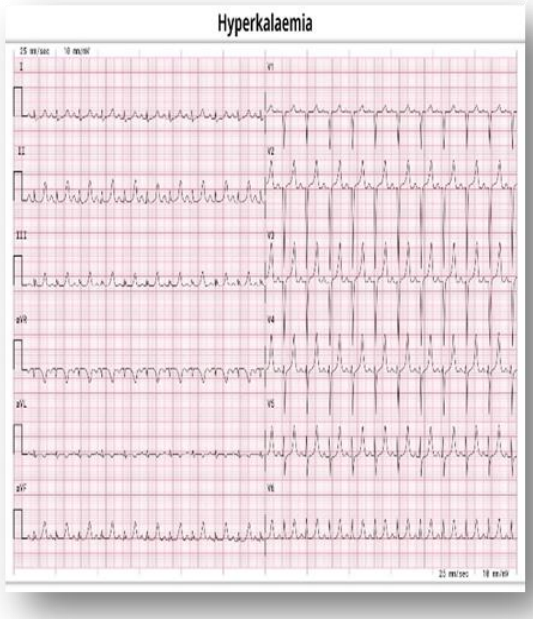
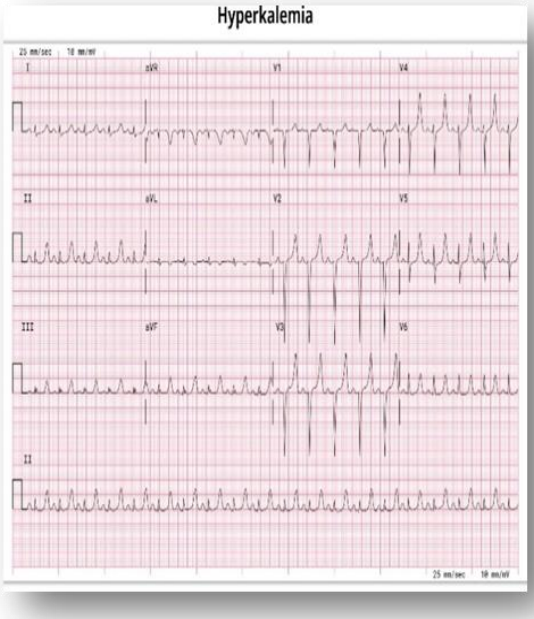


Figure No. 1: Grades of hyperkalemia.





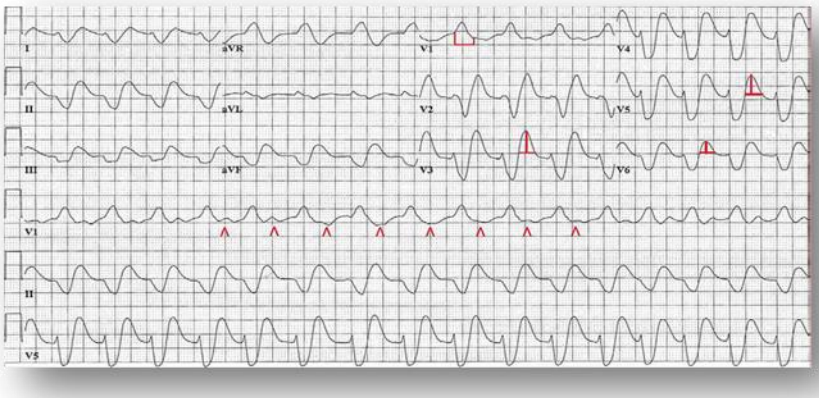


Figure No. 2: Progressive electrocardiographic changes observed in hyperkalemia.

Elevated extracellular potassium levels promote partial depolarization of the cell membrane and lower the resting membrane potential of cardiac myocytes, which results in the electrocardiographic (ECG) abnormalities seen in hyperkalemia.[11] Fast sodium channels are inactivated as a result of this ongoing depolarization, which slows impulse conduction and modifies myocardial excitability.[12] Accelerated ventricular repolarization causes tall, narrow-based, tented T waves to develop as the first ECG symptom.[13]" Atrial conduction gradually deteriorates when serum potassium levels rise, resulting in PR interval extension and P wave flattening or absence.[14] Further elevation results in delayed ventricular depolarization, which widens the QRS complex.[15] The QRS complexes combine with T waves to create a sine-wave pattern in cases of severe hyperkalemia which, if left untreated, might quickly develop into ventricular fibrillation or asystole.[16] Crucially, rapid increases in potassium are more likely to cause potentially fatal arrhythmias, and ECG symptoms may not always correspond exactly with serum potassium levels.[17]

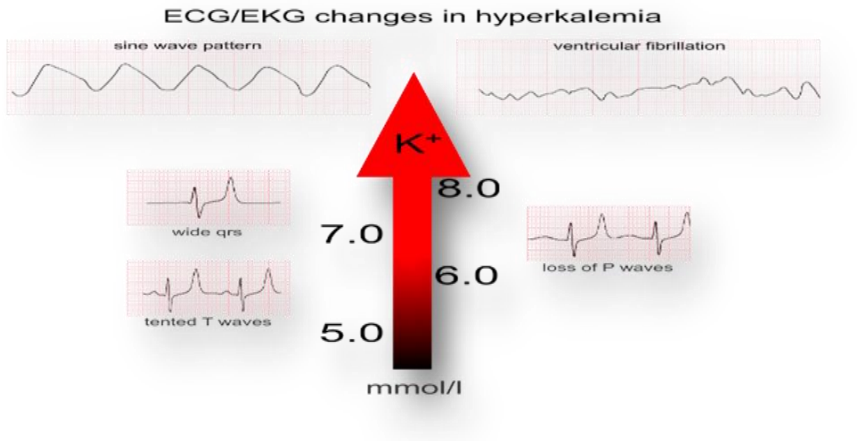


Fig. No. 3: ECG progression diagram.

MATERIALS AND METHODS

Original research studies, clinical trials, and review papers that look at the pathophysiological reasons behind hyperkalemia (HK) are included in this narrative review.[18] An organized summary of the condition was produced by analysing the chosen literature.[19] The causes causing hyperkalemia in chronic kidney disease (CKD) are discussed first, then data pertaining to risk assessment and prognosis. Lastly, a summary of the role of new potassium-lowering drugs and current management techniques is provided.[20]

Mechanisms of Hyperkalemia in Chronic Kidney Disease

In CKD, hyperkalemia is usually multifactorial. Since the kidneys are largely responsible for maintaining potassium homeostasis, impairment of renal function has a substantial impact on potassium balance.[21] Progressive nephron loss impairs the kidney's capacity to efficiently eliminate potassium in non-dialysis (ND) CKD patients, which results in increased serum potassium (sK) levels because adaptive mechanisms fail.[22]

Compensatory processes improve potassium excretion in the urine and feces in early CKD, enabling the maintenance of nearly normal sK levels. These adaptive mechanisms, however, are insufficient as renal function deteriorates, especially when the estimated glomerular filtration rate (eGFR) drops below about 20–30 mL/min. Patients are more likely to develop hyperkalemia at this point, particularly if they consume a lot of potassium through their food.[23]

One significant factor contributing to hyperkalemia in individuals with ND CKD is the extensive use of renin-angiotensin-aldosterone system inhibitors (RAASi). Because RAAS inhibitors have nephroprotective effects and can improve cardiovascular outcomes, they are advised for individuals with albuminuria. Nevertheless, these substances raise the risk of hyperkalemia by decreasing the distal nephron's aldosterone-mediated potassium excretion. Patients on RAAS inhibitors have a 5% to 40% chance of developing hyperkalemia. Losartan-treated diabetic individuals were more likely to develop hyperkalemia than placebo-treated patients, according to the RENAAL research.[24]

The preventive effects of RAAS inhibitors, such as lowering proteinuria and delaying the course of CKD, may be limited if they are reduced or stopped because of hyperkalemia. Thus, to maintain the long-term renal and cardiovascular benefits of these treatments, meticulous potassium level monitoring is required.[25]

Patients with chronic kidney disease (CKD) are more susceptible to hyperkalemia due to comorbid diseases like diabetes mellitus (DM) and heart failure. Because of decreased intracellular potassium shifting, tubular dysfunction, and poor renal potassium excretion, diabetes is thought to be an independent predictor of hyperkalemia. Reduced effective arterial blood volume in heart failure patients with chronic kidney disease (CKD) results in decreased glomerular filtration and additional impairment of potassium excretion. Concurrent use of mineralocorticoid receptor antagonists or RAAS inhibitors may make this situation worse.

All things considered, a complicated interplay between deteriorating renal function, hormone dysregulation, medication therapy, and related comorbidities causes hyperkalemia in CKD.[26]

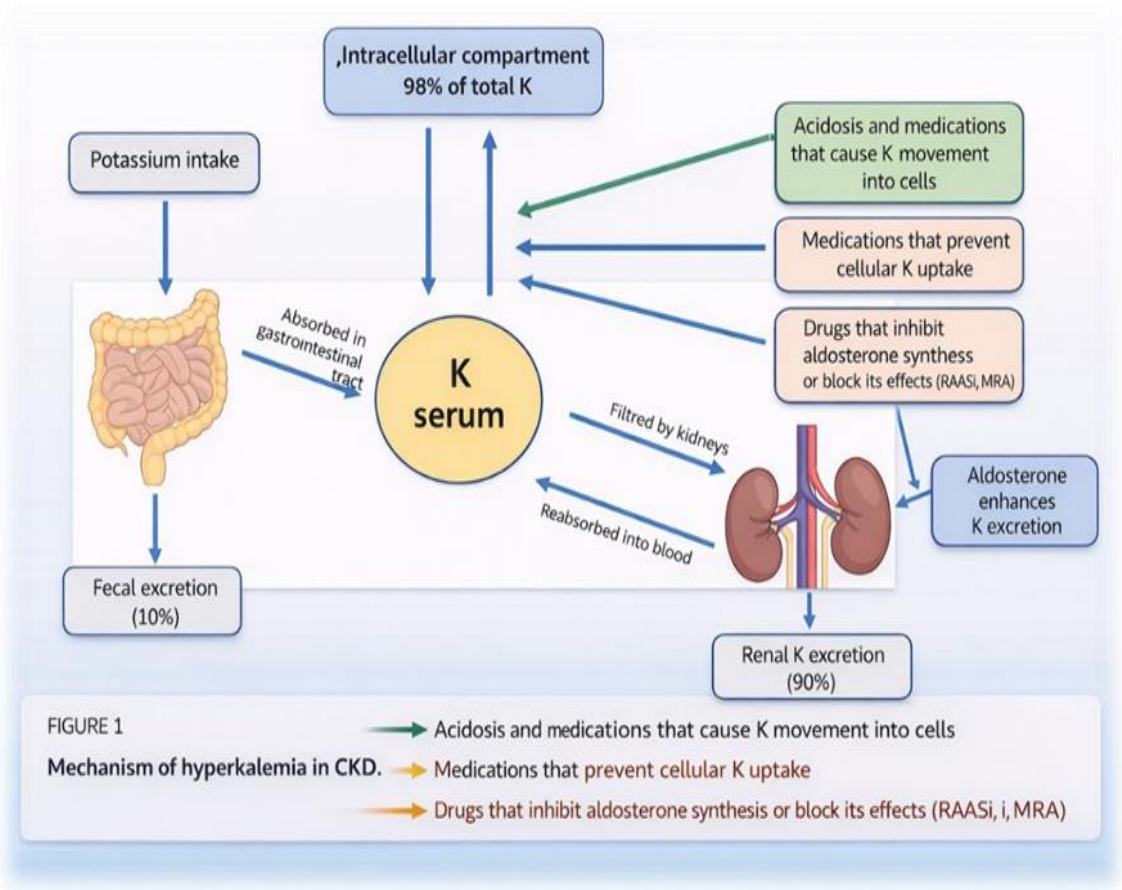
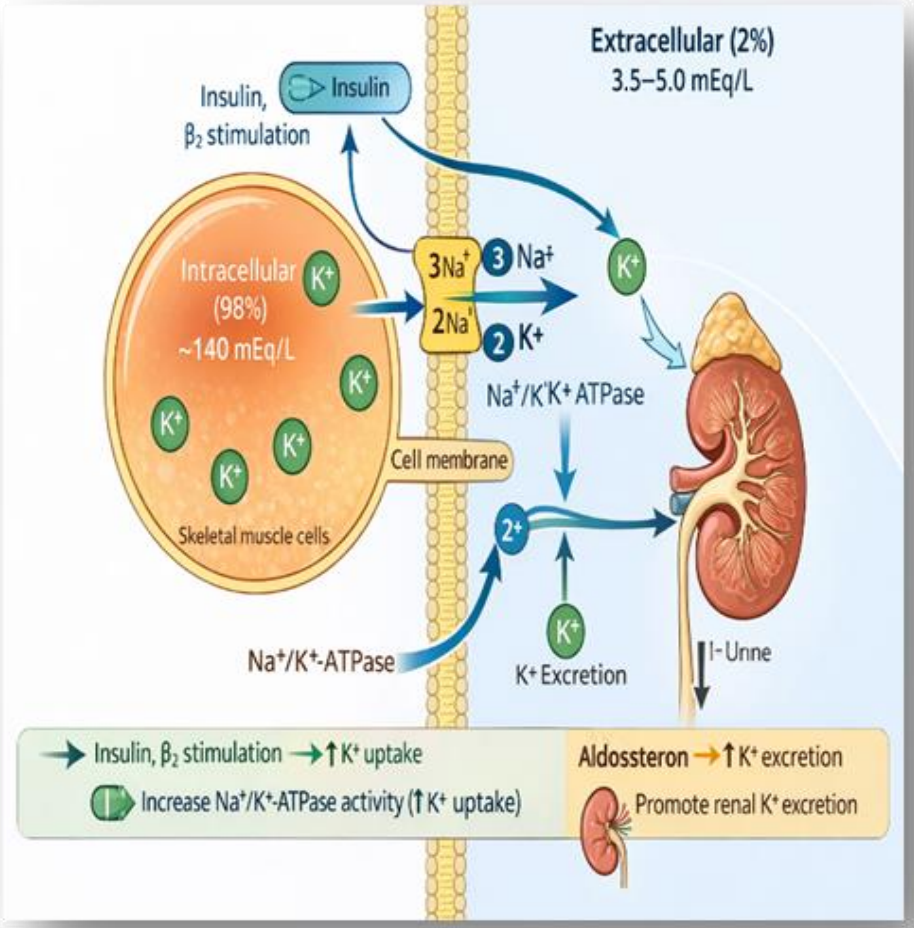


Fig. No. 4: Mechanisms of Hyperkalemia in Chronic Kidney Disease Pathophysiology of Hyperkalemia.

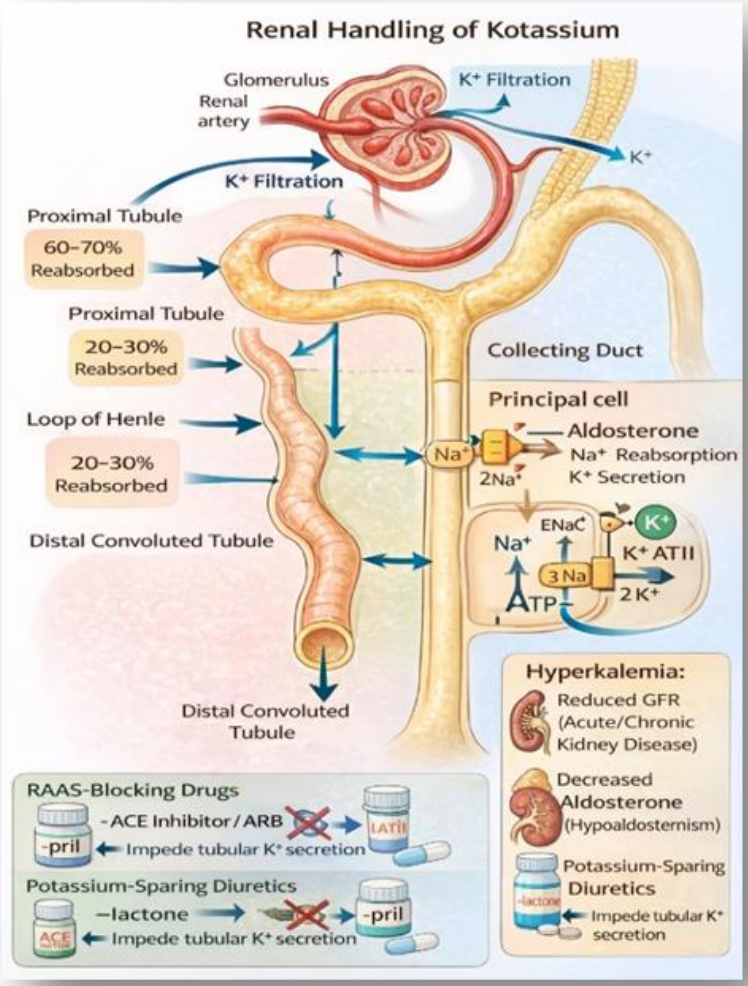
1. Potassium Distribution & Regulation



Only 2% of the potassium in the body is found in the extracellular fluid; the remaining 98% is found intracellularly, mostly in skeletal muscle cells. Serum potassium levels typically vary between 3.5 and 5.0 mEq/L. The Na+/K+-ATPase pump actively moves sodium out of cells and potassium into them, maintaining this limited range.[27]

In order to promote intracellular potassium uptake, insulin and β2-adrenergic stimulation increase the activity of Na+/K+-ATPase. Renal potassium excretion is facilitated by aldosterone. Hyperkalemia is predisposed by any imbalance in these regulatory systems.[28]

2. Renal Handling of Potassium

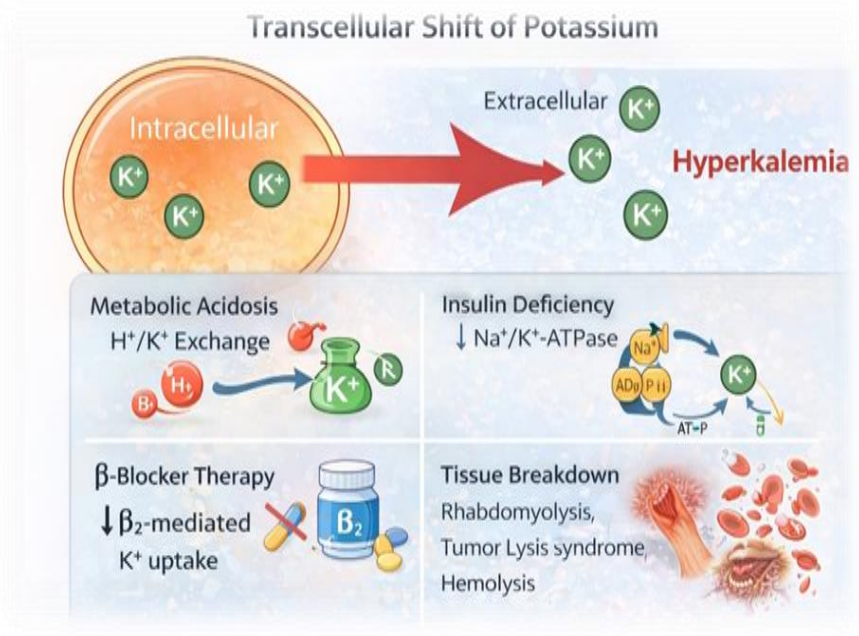


Renal control is the main factor affecting potassium homeostasis since the kidneys remove more than 90% of the potassium in the body daily.[29] Potassium is freely filtered by the glomerulus and nearly all of it is subsequently reabsorbed in the proximal tubule (about 60–70%) and the thick ascending limb of the loop of Henle (20–30%).[30] The collecting duct adistal convoluted tubule, where primary cells discharge potassium into the tubular lumen, are the sites of final regulation.[31]

Aldosterone is crucial to this process because it activates the epithelial sodium channels (ENaC) and Na+/K+-ATPase activity in main cells, which enhances potassium secretion and sodium reabsorption.[32] The rate of potassium secretion is influenced by the distal sodium supply, tubular flow rate, and aldosterone levels.[33] Hyperkalemia occurs when renal potassium excretion is impaired. Reduced glomerular filtration rate (GFR), as in acute renal

injury or chronic kidney disease, results in decreased potassium filtration and secretion.[34] Distal tubular potassium secretion is reduced by hypoaldosteronism, or decreased aldosterone production. ACE drugs and angiotensin receptor blockers, which target the renin-angiotensin-aldosterone system (RAAS), further impair aldosterone-mediated potassium excretion. Potassium-sparing diuretics further reduce distal potassium secretion by blocking ENaC or antagonistically binding to aldosterone receptors, increasing the risk of hyperkalemia.[35]

3. Transcellular Shift of Potassium



Even in the absence of a general excess of potassium in the body, hyperkalemia can result from the movement of potassium from the intracellular to the extracellular compartment[1]. Since approximately 98% of the potassium in the body is located inside cells, even a small migration outward can significantly increase serum potassium levels.[36]

Metabolic acidosis is the primary source of transcellular potassium shift.[37] Potassium ions are transported out of cells to maintain high extracellular potassium levels hydrogen ions and electroneutrality enter cells for buffering in educational settings.[38] Insulin deficiency also leads to hyperkalemia because it inhibits the Na+/K+-ATPase pump, which reduces intracellular potassium uptake.[38] Similarly, β_2-adrenergic stimulation improves cellular potassium uptake, while β-blocker medications hinder this process, resulting in decreased potassium entry into cells and higher serum potassium concentration.[39]

Significant amounts of intracellular potassium are released into the bloodstream by tissue

breakdown disorders such haemolysis, tumor lysis syndrome, and rhabdomyolysis, which can potentially cause acute hyperkalemia.[40] These procedures show that decreased renal excretion and changed cellular potassium distribution can both lead to hyperkalemia.[41]

Treatment of Hyperkalemia

The step-by-step treatment approach for hyperkalemia based on electrocardiogram (ECG) results and clinical severity is indicated in the diagram.[42] The initial evaluation includes an analysis for anomalies in the ECG and confirmation of elevated serum potassium. Patients with severe hyperkalemia or cardiac symptoms should immediately stabilize their myocardial membranes with intravenous calcium salts to reduce the risk of arrhythmias. When necessary, β-adrenergic agonists, insulin with glucose, and sodium bicarbonate are used to temporarily shift potassium into the intracellular compartment.[43] The last course of treatment involves utilizing diuretics to increase renal excretion and gastrointestinal potassium-binding medications to remove potassium from the body. or haemodialysis in cases that are severe or resistant. To prevent recurrence, precipitating factors must be identified and corrected, along with medication reviews and concurrent disease care. This systematic approach integrates acute stabilization with long-term therapeutic approaches to optimize patient outcomes.[44]

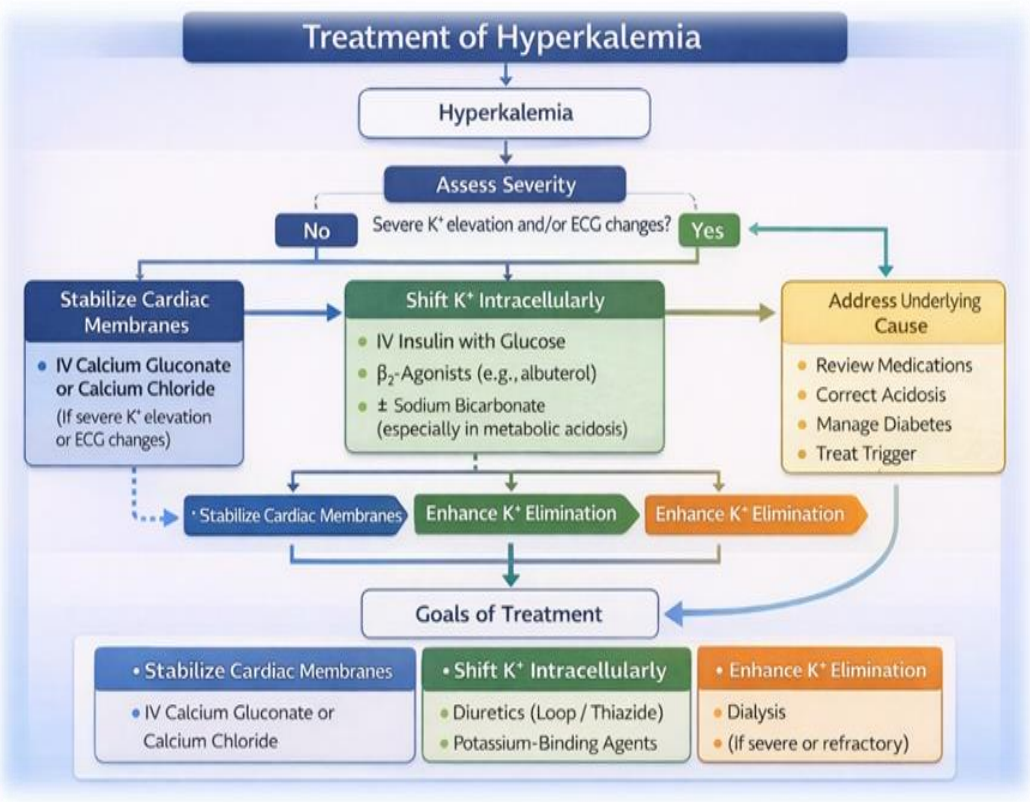


Fig. No. 5: Treatment of hyperkalemia.

CONCLUSION

If not detected and treated right once, hyperkalemia, a clinically significant electrolyte imbalance, can cause serious and even fatal consequences, especially cardiac arrhythmias. Patients with diabetes mellitus, heart failure, chronic kidney disease, and those using drugs that affect potassium regulation—particularly renin-angiotensin-aldosterone system inhibitors—are frequently found to have the syndrome.[45] A major contributing factor to the development of hyperkalemia is impairment in renal excretion and intracellular–extracellular distribution, which regulate potassium homeostasis to a considerable extent.

Reduced renal potassium clearance, hormonal abnormalities such aldosterone resistance or shortage, transcellular potassium shifts, and elevated potassium load in vulnerable people are all part of the complicated and usually multivariate pathophysiology of hyperkalemia.[46] The risk is significantly increased by a progressive loss in renal function, especially when compensatory mechanisms are no longer adequate. Additionally, drug-induced hyperkalemia constitutes a serious therapeutic problem, especially in patients requiring long-term cardioprotective and nephroprotective therapy.[47]

To avoid negative clinical outcomes, early risk factor identification, vigilant serum potassium level monitoring, and electrocardiographic change detection are crucial. Stabilization of cardiac membranes, temporary potassium redistribution into cells, and the final elimination of excess potassium from the body should all be part of a methodical management strategy. Preventing recurrence requires addressing underlying reasons, managing comorbid diseases, and making the right drug adjustments. The capacity to manage chronic hyperkalemia has increased with the advent of novel potassium-binding drugs, enabling the continuation of helpful treatments like RAAS inhibitors.[48]

All things considered, an integrated clinical approach combining pathophysiology knowledge, prompt diagnosis, and customized treatment plans is necessary for the optimal management of hyperkalemia. The morbidity and mortality linked to this illness can be considerably decreased by raising clinical awareness and putting preventative measures into place. Patient outcomes may be further improved by future studies that concentrate on safer treatment alternatives and better risk prediction algorithms.[49]

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