Review Article

Approach to Hypokalemia

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ABSTRACT

Hypokalemia, serum K^+ less than 3.5 mmol/L is most common electrolyte abnormality noted in practice in upto 21% of hospitalised patients. More than 98% of total body potassium is intracellular, and a mere 2% reflects serum potassium. Changes in distribution of intra & extracellular K^+ or depletion of total body K^+ is what causes hypokalemia. Potassium is subject to renal, enteral & hormonal regulation namely by insulin, catecholamines, thyroxin causing intracelluar movement of K^+ leading to redistributive hypokalemia and to a lesser extent secretion of aldosterone which causes renal excretion of K^+. Hypokalemia is essentially asymptomatic until serum K^+ goes below 2.5 mmol/L, when it can have various manifestations ranging from generalized weakness, skeletal myopathy, constipation to respiratory paralysis & life threatening arrythmias. ECG showing U wave with prolonged QU interval (pseudo QT) is essential for diagnosing severe hypokalemia. History to rule out decreased intake or drug intake with bedside clinical examination to check for cushing's syndrome or hyperthyroidism along with laboratory investigations like ABG, TTKG, 24-hour urinary K^+, urinary chloride and urine diuretic screening, aid in diagnosing the cause of hypokalemia. Urgent correction is required in moderate to severe hypokalemia with oral route preferred over intravenous with special emphasis to prevent rebound hyperkalemia. Continuous cardiac monitoring is adviced when infusion rates exceed 10 meq/Hr.In cases of refractory hypokalemia correction of hypomagnesemia corrects hypokalemia.

Introduction :

Low serum potassium is the most common electrolyte abnormality encountered in daily practice, defined by serum K^+ level less than 3.5 mmol/l. Upto 21% of hospitalised & 2-3% of out patients develop hypokalemia; with about 5.2% having serum K^+ less than 3 mmol/l.[1] Both hypokalemia and hyperkalemia is associated with increased mortality in heart failure.[2] In a healthy individual, the entire daily intake of potassium is excreted, 90% through urine; 10% in stool. The total body potassium in healthy 70 kg adult is ~3500 mEq; > 98% of total body potassium is intracellular, chiefly in muscle and a mere 2% reflects in serum potassium concentration. Changes in distribution of intra & extracellular K^+ or depletion of total body K^+ is what causes hypokalemia.

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CLINICAL FEATURES OF HYPOKALEMIA

Hypokalemia has prominent effect on cardiac, skeletal, intestinal muscle cells. Symptoms of hypokalemia seldom occur at serum K^+ more than 2.5 mmol/L.[3] As the hypokalemia worsens to less than 2.5 mmol/L, K^+ accumulation into the interstitial space is blunted, thus impairing skeletal muscle blood flow and contributing to skeletal myopathy & rhabdomyolysis; presenting with generalised weakness, lassitude, constipation. Hypokalemia causes skeletal hyperpolarisation which impairs skeletal contraction ensuing muscle paralysis. Level less than 2 mmol/L are associated with ascending paralysis with eventual respiratory impairment. Paralytic effect on intestinal smooth muscle causes paralyticileus. More than 50% of the patients with severe hypokalemia have ECG changes.[4] First manifestation being decrease in amplitude of T wave and appearance of U wave which is followed by ST segment sagging and T wave inversion. It leads to PR prolongation. Amplitude of U wave exceeds T wave when serum K^+ level is less than 3 mmol/L. With further fall in serum potassium there is fusion of U wave and T wave forming a large U wave with pseudo prolongation of QT interval which is actually QU

interval with absent T wave.[5] Hypokalemia promotes both systolic and diastolic hypertension when sodium intake is unrestricted, by promoting renal sodium retention. $K^+ < 3.5$ mmol/L reduces repolarization reserve by directly inhibiting K^+ channel conductances and indirectly by suppressing Na^+ - K^+ ATPase which promotes early after depolarization (EAD), delayed-after-depolarisation (DAD), and after-depolarization-mediated arrhythmias. Reduced repolarization reserve predisposes the heart to EADs and EAD-mediated arrhythmias, including Torsades de pointes and polymorphic ventricular tachy cardia (VT), which can degenerate to ventricular fibrillation (VF) causing sudden cardiac death, especially in patients with genetic or acquired causes of long QT syndrome.[6] Functional effect of hypokalemia on kidney includes Na^+, Cl^- and HCO 3 retention, polyuria, hypocitraturia, renal ammoniagenesis.[7] Bicarbonate retention causes metabolic alkalosis. Potassium is recycled via the apical ROMK channel, which facilitates ongoing sodium reabsorption in the thick ascending limb (TAL) and maintenance of the medullary concentration gradient. Therefore, potassium deficiency may lead to concentrating defects via this pathway, leading to polyuria. There is also some evidence that hypokalaemia leads to impaired responsiveness to ADH. In the setting of hypokalemia the movement of potassium out of cells in the proximal tubule is balanced by inward movement of hydrogen ions. The creation of an intracellular acidosis increases ammonia production by the proximal tubular cells, which may exacerbate problems in patients with decompensated liver disease. Chronic potassium depletion (over a month at least) in humans can cause the development of vacuolar lesions in renal epithelial cells, primarily in the proximal tubule. If the deficiency persists over a longer time period, changes including interstitial nephritis, tubular atrophy and medullary cyst formation have been described. Potential mechanisms underlying these changes may be related to altered growth factor and cytokine production, or ammonia accumulation. This collection of findings has loosely been referred to as hypokalemic nephropathy.

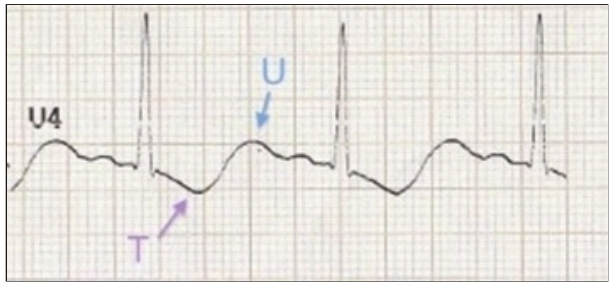


Fig. 4 : **T wave inversion with appearance of U wave**

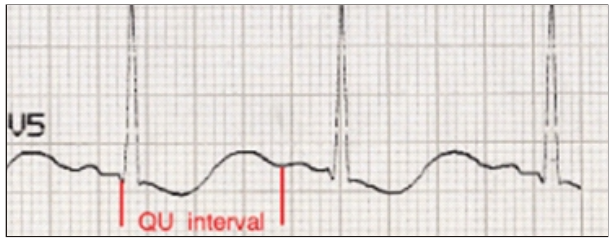


Fig. 5 : **Long QU interval in hypokalemia**

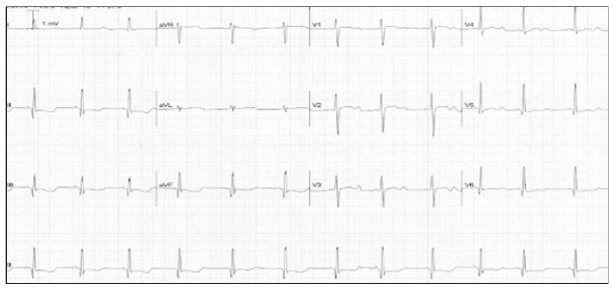


Fig. 6 : **ECG of a patient with serum K^+ 1.7 mmol/L suggestive of ST segment depression, Twavein version, appearance of prominent U waves & long QU interval.**

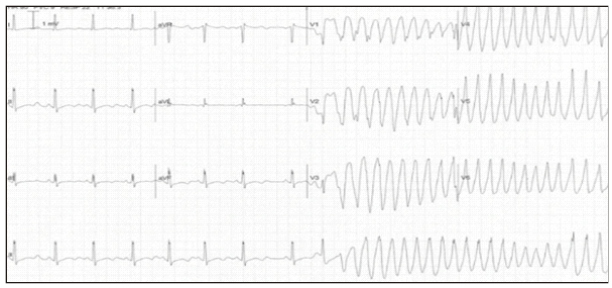


Fig. 7 : **Severe hypokalemia leading to Torsades se pointes.**
Note the atrialectopic with 'R on T' or 'R on U' that initiates paroxysm of TdP.

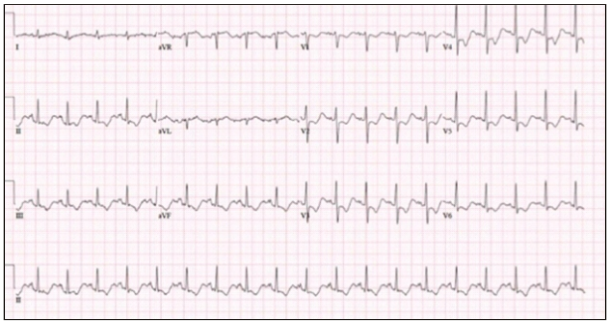


Fig. 8 : **ECG of a patient with serum potassium 2.3 mmol/L. Note the widespread ST segment depression, Twavein version, prominent U wave appearence with pronlongation of QU interval.**

Causes of Hypokalemia :

Transient causes of hypokalemia are due to cell shift, whereas sustained hypokalemia can be manifested by either inadequate intake or excessive K+ loss. Hypokalemia resulting from excessive K+ loss can be due to renal or extrarenal losses.

A) Due to Decreased Intake -

Anorexia nervosa, crash diets, alcoholism, and intestinal malabsorption are clinical situations associated with K^+ deficiency. Even with a diet deficient in K^+, kidney can restrict the excretion of urinary potassium to ~ 15 mmol/dl, not below. The amount of dietary K^+ required for normal homeostasis has been reviewed by the Food and Nutrition Board of the Institute of Medicine and has been adviced as upto 4,700 mg/day.[8] Studies demonstrate that the mean intake in US for women was estimated to be 2,290 mg/day, and 3,026 mg/day for men[9] which is much below than required. FDA has now designated K^+ as a "nutrient of public health concern" because of insufficient dietary intake.[10] High dietary K^+ has been linked to reducing blood pressure, decreasing the risk of stroke, improving bone health, and reducing the risk of nephrolithiasis.[11]

B) Due to Redistribution Into Cells -

1) Hormonal Causes -

Rapid changes in extracellular K^+ levels are a manifestation of movement of K^+ in and out of cell in comparison to the gradual changes in renal K^+ excretion. Metabolical kalosis causes increased movement of potassium into cell. Insulin and increased beta 2 sympathomimetic activity due to catecholamines urge states like post myoardial infarction, alcohol withdrawal, head injury also cause increased cellular uptake of K^+ by stimulating cell membrane Na^+/K^+ ATPase pump.[3] Thyrotoxic periodic paralysis is another condition in which redistributive hypokalemia occurs in a hyperthyroid state, seen more in patients of asian and hispanic origin due to genetic variation in Kir 2.6, a thyroid hormone responsive K^+ channel. Hypokalemia here is almost always is associated with hypophosphataemia and hypomagnesemia. Hypokalemia here is also attributed to direct and indirect (increasing adrenergic activity) activation of Na^+/K^+ ATPase.[12]

2) Drug Related Causes -

2-Sympathomimetic Drugs includes drugs like decongestants, bronchodilators, and inhibitors of uterine contraction. A standard dose of nebulized albuterol reduces serum potassium by 0.2 to 0.4 mmol per liter, and a second dose taken within one hour reduces it by almost 1 mm ol/L.[13,3,14] Intentional ingestion of excess amounts of pseudoephedrine can cause severe hypokalemia. Ritodrine and terbutaline, inhibitors of uterine contraction, can reduce serum potassium to as low as 2.5 mmol/L after four to six hours of intravenous administration.[15] Xanthines including Theophylline and caffeine are not sympathomimetic drugs, but these agents stimulate the release of sympathetic amines and may also increase Na^+/K^+ ATPase activity by inhibiting cellular phosphodiesterase. Severe hypokalemia is an almost invariable feature of acute theophylline toxicity.[16]

3) Other -

Familial hypokalemic periodic paralysis caused by missense mutation of voltage sensor domains within alpha1 subunit Ltype calcium channel (60%) or skeletal Na+ channel (20%). Homologous gene defects of either channel cause an anomalous leakage current, which is active at the resting potential and produces

Table 1 : **List of Drugs that Cause Hypokalemia**

HYPOKALEMIA DUE TO TRANSCELLULAR POTASSIUM SHIFT	● B_2 ADRENERGIC AGONIST- Epinephrine
	● DECONGESTATNTS-Pseudoephedrine, Phenylpropanolamine
	● BRONCHODILATORS-Salbutamol, Terbutaline, Ephedrine, Isoproterenol
	● TOCOLYTICS-Ritodrine, Nylidrine
	● Theophylline
	● Caffeine
	● Verpamil intoxication
	● Chloroquin intoxication
	● Insulin Overdose
HYPOKALEMIA DUE TO INCREASED RENAL POTASSIUM LOSS	● DIURETICS - Furosemide, Thiazides, Acetazolamide
	● MINERALOCORTICOID - fludrocortisone
	● SUBSTANCES WITH MINERALOCOTICOID ACTIVITY -Licorice, Carbenoxolone, Gossypol
	● HIGH DOSE GLUCOCORTICOIDS
	● HIGH DOSE ANTIBIOTICS - Penicillin, Naficillin, Carbenicillin
	● DRUGS CAUSING Mg2 + DEPLETION - Aminoglycoside, Cisplatin. Foscarnet, Amphotericin B
HYPOKALEMIA DUE TO INCREASED LOSS IN STOOL	● PHENOLPTHALEIN
	● SODIUM POLYSTERENE SULPHONATE

susceptibility to paradoxical depolarization of the fiber and inexcitability in the setting of low extracellular K^+ (2.5 to 3.5 Meq/L).[17] Accidental Barium ingestion prevents free K^+ exit from cells causing hypokalemia.[18]

C) Due To Increased Loss - ***1) Renal -***

Table 2 : **Renal Causes of Hypokalemia**

A] INCREASED DISTAL FLOW AND DISTAL SODIUM DELIVERY	1. DIURETICS 2. OSMOTIC DIURETICS 3. SALT WASTING NEPHROPATHIES
B] INCREASED SECRETION OF POTASSIUM	**1) MINERALOCORTICOID EXCESS :** A. PRIMARY HYPERALDOSTERONISM B. GENETIC HYPERALDOSTERONISM (FH TYPE 1/2/3 OR CONGENITAL ADRENAL HYPERPLASIA) C. SECONDARY HYPERALDOSTERONISM (MALIGNANT HTN, RENIN SECRETING TUMOR, RENAL ARTERY STENOSIS, HYPOVOLEMIA) D. CUSHING'S SYNDROME E. BARTTER'S SYNDROME F. GITELMAN'S SYNDROME
	2) APPARENT MINERALOCORTICOID EXCESS : A. GENETIC DEFICIENCY OF 11?- DEHYDROGENASE-2 (SAME) B. INHIBITION OF 11?- DEHYDROGENASE -2 (LICORICE,GLYCYRRHIZINIC ACID) C. LIDDLE SYNDROME
	3) DISTAL DELIVERY OF NONABSORBABLE ANIONS : A. VOMITING B. PROXIMAL RENAL TUBULAR ACIDOSIS C. DIABETIC KETOACIDOSIS D. PENICILLIN DERIVATIVES E. GLUE SNIFFING (TOLUENE)

2) Non Renal - Gastrointestinal loss associated with diarrhea or through profuse sweating.

Table 3 : **Gastrointestinal Causes of Hypokalemia**

1	INFECTIVE DIARRHOEA- Cholera, Salmonella, Strongyloids, Yersinia, Diarrhoea associted with AIDS
2	TUMOR- VIPoma, Villous adenoma of colon, Zollinger-Ellison syndrome
3	JEJUNOILIAL BYPASS
4	ENTERIC FISTULA
5	MALABSORPTION
6	CONGENITAL CHLORIDE DIARRHOEA
7	CANCER THERAPY Chemotherapy, Radiation Enteropathy
8	GEOPHAGIA

D) Magnesium Deficiency -

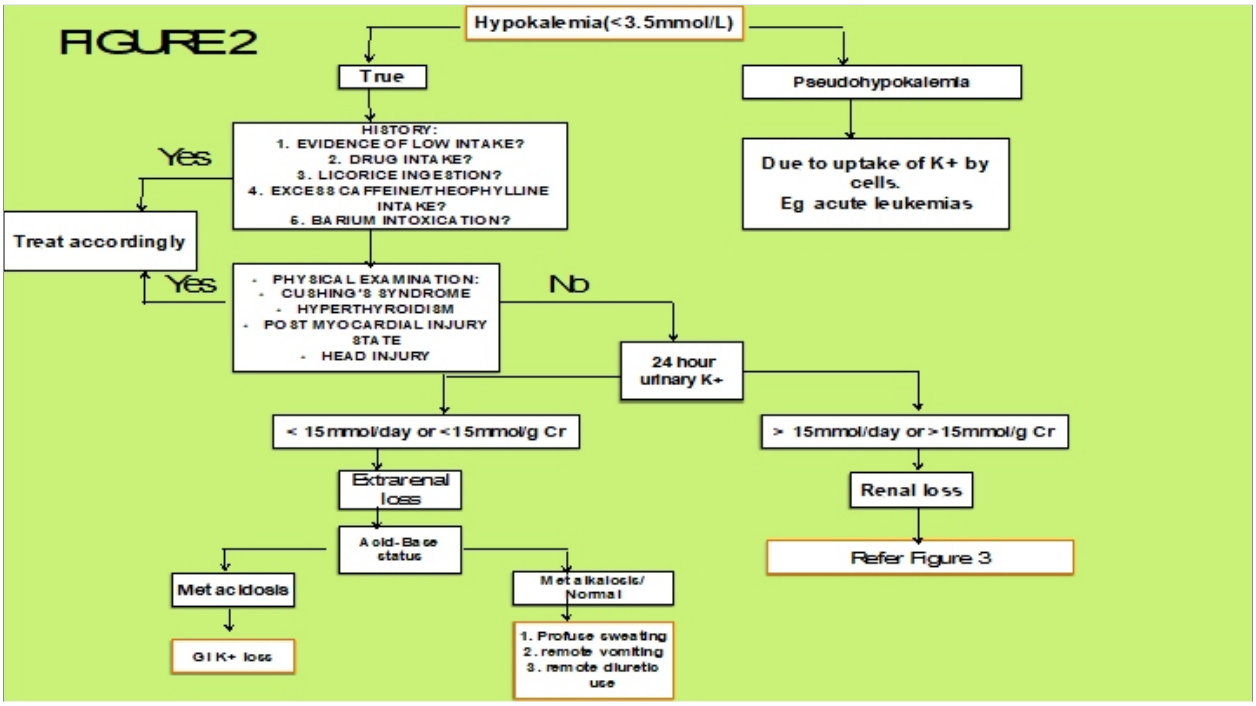
Magnesium deficiency may contribute to the observed hypokalemia. In such a state it is refractory to treatment due to a persistent increase in renal K^+ excretion, since intracellular Mg^{++} normally inhibits K^+ secretion through the ROMK channel in the distal nephron[19] such that hypokalemia is refractory to treatment until the $Mg2^+$ deficit is repaired. The kaliuretic effect induced by magnesium deficiency is further exacerbated under conditions of increased distal Na^+ delivery and increased aldosterone.

Diagnostic Approach :

A clinical algorithm can be followed after thorough history on medication (laxative, diuretics, antibiotics), dietary habits (licorice) and or symptoms (diarrhea, periodic weakness). Examination to rule out any endocrinal disorder (Cushing's syndrome, hyperthyroidism), assess volume status and blood pressure. One should start with electrolytes, urea, creatinine, serum osmolality, $Mg2^+$, $Ca2^+$, complete blood count, urinary pH, osmolality, creatinine, electrolytes. Renal potassium excretion can be assessed by measuring 24-hour urinary K^+ of < 15 mmol/l indicating extrarenal loss. If only random spot sample is available, serum and urine osmolality can be used to calculate Transtubular K^+ gradient (TTKG), which should be less than 3 in hypokalemic state. Also, urinary K^+-to-creatinine is compatible with excessive renal K^+ excretion. Urinary Cl- is decreased in patients with hypokalemia secondary to nonabsorbable ions (penicillin / hippurate) or bicarbonate. Urinary diuretic screen can be done to rule out loop / thiazide abuse. Other testes like thyroid function test, Plasma renin activity (PRA), aldosterone can be done in specific situatons. A ratio of PRA and aldosterone greater than 50 is suggestive of hyperaldosteronism. Further genetic testing to find the cause of primary hyperaldosteronism (Familial hyperaldosteronism, Liddle's syndrome, SAME).

Principles of Management of Hypokalemia :

Goals of management are to prevent any life-threatening consequences. Optimum treatment of hypokalemia requires that the cause be established and the underlying disorder alleviated. Establishing whether hypokalemia is caused by a transcellular shift or by a K^+ deficit is essential. K^+ disturbances almost invariably feature acid base disorders (HPP is an exception), the acid base status should be investigated. If the patient has metabolic acidosis (for example, from distal renal tubular acidosis), the hypokalemia should be treated before the acidosis is addressed.[20] Urgent treatment needs to be initiated when K^+ is < 2.5 mM. If replacement needs to be given intravenously, it is safer not to exceed a dose of 20 mmol/h, as there is a danger of rebound hyperkalemia. In conditions with excessive sympathetic over activity causing redistributive hypokalemia (TPP, Theophylline overdose, acute head injury), high dose propranolol (3 mg/kg) should be considered as it prevents rebound hyperkalemia.[21] In retrospective studies by Manoukain[22] and Lin[23] and colleagues, rebound hyperkalemia occurred in 30% to 42% of patients with HPP, especially if more than 90 mmol of



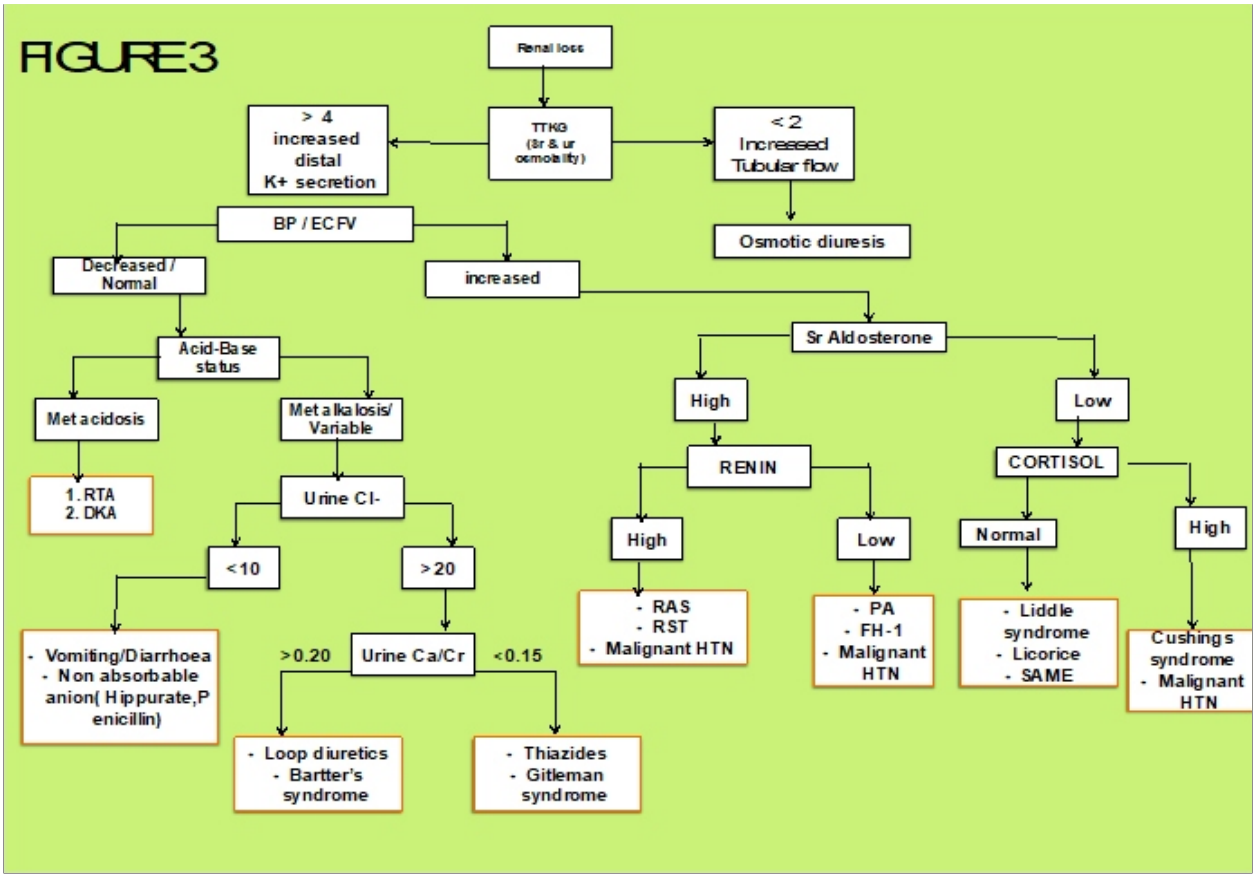


Fig. 2 & 3 : **Flow Chart Showing Diagnostic Approach to Hypokalemia**

potassium chloride was given within 24 hours. In patients with HPP, the dose of potassium chloride supplementation should be minimal (10 mmol/h) to avoid rebound hyperkalemia.[24]

Serum potassium levels do not correlate well with intracellular potassium levels and may not correlate with total body potassium.[25] Therefore, hypokalemia may not imply a depletion of body potassium stores. Potassium supplementation and dosing are largely empirical and guided by serum potassium levels. Oral replacement with K^+ CL^- is preferred over intravenous therapy. Intravenous Potassium supplementation (as chloride, acetate, or phosphate salts) is reserved for the treatment of severe symptomatic hypokalemia (paralysis, arrhythmia) or when the enteral route cannot be used. Oral potassium supplements are available as chloride, bicarbonate, citrate, gluconate, and phosphate salts. The most commonly used oral or i.v. supplement is potassium chloride. Potassium acetate and bicarbonate can be used when the correction of acidemia is also desired. Potassium phosphate is used to correct coexisting hypokalemia and hypophosphatemia. Oral potassium dosages of 40-100 meq daily are usually sufficient to correct hypokalemia. The total daily dosage should be divided into two to four doses to avoid adverse GI effects. An oral potassium dosage of 20 meq daily has been suggested to prevent hypokalemia in patients receiving chronic diuretic therapy.[26] An initial intravenous potassium dose of 20-40 meq diluted in normal saline for an ICU patient with mild to moderate hypokalemia (serum potassium concentration = 2.5-3.4 meq/L) is advisable.[27] Potassium should never be administered as a rapid infusion because of the risk of serious or fatal consequences. Intermittent potassium dosing can be safely achieved at potassium infusion rates of 10-20 meq/hr. If an infusion rate exceeding 10 meq/hr is needed, continuous cardiac monitoring is recommended to detect any signs of hyperkalemia, and infusion via a central venous catheter is recommended to minimize infusion related burning and phlebitis. In critical situations, infusion rates as high as 40 meq/hr have been used but should be reserved for emergent cases or symptomatic patients. Total daily potassium supplementation should not exceed 240-400 meq/day. Potassium concentration in solutions for continuous infusion via a peripheral vein should be limited to 80 meq/L. Potassium concentrations of up to 120 meq/L can be used for central-vein infusion.[28] Serum potassium levels should be monitored frequently (every 1-6 hours) in patients with severe hypokalemia if symptoms are present or if aggressive i.v. treatment is ongoing. Monitoring of serum potassium after i.v. repletion in ICU patients with mild to moderate hypokalemia (within 2-8 hours) may be appropriate, in addition to routine monitoring. Femoral veins are preferred over internal jugular or subclavian central lines as it can increase local potassium concentration and affect cardiac conduction. Preventive measures to minimize losses namely reducing dose of non-K+- sparing diuretics, restricting sodium intake should be practiced. Hypomagnesemia causes refractory hypokalemia, in such cases correction of hypomagnesemia via oral or i.v route alone corrects hypokalemia.

Conclusion:

There are multiple modalities available to correct hypokalemia, including I.V. and / or oral supplementation, along with correction of the primary abnormality that resulted in loss of potassium in the first place, such as reducing the dose of non-potassium sparing diuretics in patients with cardiac failure, restriction of sodium intake and limited use of bronchodilators. A systematic approach based on primary etiology and patient response to treatment may lead to rapid recovery and satisfactory outcomes.

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