Potassium is an important ion in body, which is required for functions of cells, especially nerve and muscle cells. It comes in body through food and the kidneys remove excess of potassium to keep a proper balance of mineral in the body. Hypokalemia is a disorder that occurs when the serum potassium (Sk) in the blood drops to < 3.5 mEq/L.

**PHYSIOLOGY**

Daily potassium load is 50-150 mEq out of which 90% is excreted in urine and remaining through stool and sweat. When renal function is compromised, the GI tract can eliminate up to 30% of the intake; enteric loss of potassium in diarrheal conditions can be substantial. K secretion by colon and sweat gland is stimulated by aldosterone.

Sk is a general indicator of total body potassium. However, because only about 2% of total body K is in the extracellular fluid and 98% is in the cells, small losses or gains by the cells can cause large changes in Sk.

**ACID-BASE BALANCE**

Metabolic acidosis promotes hyperkalemia whereas alkalosis promotes hypokalemia.

**INSULIN**

Insulin deficiency impairs cellular K uptake and promotes hyperkalemia, probably through the lack of stimulation of Na-K-ATPase. Increased Sk stimulates pancreatic insulin release while hypokalemia has an inhibitory (diabetogenic) effect.

**CATECHOLAMINES**

Catecholamines, particularly beta-2 agonists e.g. terbutaline, stimulates the cellular Na-K pump and can result in moderate hypokalemia.

**ALDOSTERONE**

Aldosterone stimulates cellular potassium uptake and facilitates renal K excretion. It stimulates Na-K pump, not only in the renal collecting ducts, but in other organs as well.

**RENAL REGULATION OF POTASSIUM (FIGURE 1)**

Almost 90% of the K eliminated in the urine is due to secretion in the cortical collecting duct. It is influenced by conditions like adrenal insufficiency, hyperaldosteronism and Cushing’s syndrome. K secretion by the collecting duct is stimulated by high Sk, increased tubular fluid flow and diuretics. Reduction in the dietary K intake results in renal conservation of K both by decreasing K secretion in the cortical collecting duct and enhancing reabsorption in the medullary collecting duct.

**WHAT ARE THE CAUSES OF HYPOKALEMIA?**

Renal losses: diuretics (loop and thiazide), renal tubular acidosis (RTA), excess aldosterone

GI losses: diarrhea, laxative abuse, villous adenoma
Approach to Hypokalemia

Alkalosis: hydrogen ions transported out of cells at the expense of K⁺ flowing in

Manifestations of hypokalemia include:
- Muscle weakness, cramps, tetany
- Fatigue
- Constipation, ileus
- Arrhythmias and predisposition to digitalis toxicity
- Muscle damage, rhabdomyolysis
- Paralysis (which can include the lungs)
- ECG changes: T wave flattening, U waves, ST segment depression
- Renal: Polyuria (nephrogenic diabetes insipidus), polydipsia

**APPROACH TO A PATIENT WITH HYPOKALEMIA:**

**History:**
The search for etiology of hypokalemia should begin with a careful history and physical examination concentrating on the drug history and the state of hydration (vomiting and diarrhea).

**DURATION OF SYMPTOMS**
What is meant by weakness? Is it focal neurological or generalized? Rule out symptoms like cough, shortness of breath, diarrhea, vomiting, fasting, dysuria, fever etc which can account for lethargy.

Past history: Similar episodes or neurological disease or renal disease?

Drug history: diuretics, laxatives, alternative or recreational medicines

Personal history: constipation, smoking, alcohol

Family history: renal disease, periodic paralysis, neurological problems

**Investigations on initial assessment:** after careful examination which includes assessment of hydration, BP and neurological examination, following investigations are asked for: CBC, Routine urinalysis, Urinary electrolytes on a spot sample (urine sample must be collected before treatment is started for correction of Sk), renal and liver function tests, CRP, ECG, CXR, ABG

**Additional tests which are useful:** Serum magnesium level, Aldosterone, Renin and Cortisol levels

It is first necessary to determine whether hypokalemia is an emergency or non emergency. It is also important to find out whether hypokalemia is artefactual, the result of redistribution of K⁺ or a result of true K depletion. Artefactual values may be seen in leukemic patients with a WBC value > 100,000/mm³. The clinical setting and the blood pH will determine whether hypokalemia is secondary to redistribution.

Once these are ruled out, start with urinary K values.

If urinary K is <15mEq/d: Look at ABG.

If metabolic acidosis: diarrhea, GI fistula, fasting/starvation.

If neutral pH: profuse sweating, inadequate intake.

If metabolic alkalosis: remote vomiting or remote diuretics.

If variable pH: laxative abuse, villous adenoma.

If urinary K is > 15 mEq/d, estimate TTKG.

**TTKG** = \( \frac{\text{Urine K}}{\text{Serum K}} \times \frac{\text{Urine Osm}}{\text{Serum Osm}} \)

**DEFINITION**
A calculated measurement which estimates the tubular fluid potassium concentration at the end of the cortical collecting tubule, the site responsible for most of potassium secretion. In simplest terms, think of the TTKG as a rough measurement of aldosterone activity in the kidney. TTKG = 8-9 in normal subject on a normal diet

**PRACTICAL APPLICATION**
Hyperkalemia (typically persistent high Sk)

Use the TTKG to determine if high K⁺ is from low aldosterone states or from decreased effective circulating volume (in CHF,
In low aldosterone states, K+ in the cortical collecting tubule should be low and thus the TTKG should be low.

If hypoaldosterone state, TTKG < 5
If decreased ECV, TTKG > 7

Hypokalemia (Persistent)
Use the TTKG to determine renal vs. non-renal loss of potassium.
If loss is renal, assume hyperaldosterone state and thus K+ at the cortical collecting duct should be high and thus the TTKG should be high.
If renal loss of K+, TTKG > 7
If non-renal loss, TTKG < 5 (should be hypoaldo from low K+)

Simply think of the TTKG as a rough measurement of aldosterone activity in the kidney. As aldosterone’s action is retention of Na with excretion of K, tubular fluid K concentration is high if there is aldosterone action, and so is TTKG. Division by (urine osmo/plasma osmo) is to adjust the urinary potassium for the concentrating effects that occur in the collecting tubule, where water is removed from the urine. Note that this formula is valid only when Uosm >300 and UNa >25. A high TTKG suggests that the kidney is wasting potassium, which may be appropriate (in the setting of hyperkalemia) or inappropriate (in the setting of hypokalemia). Normally, hypokalemia should produce a TTKG < 3. The expected TTKG in hyperkalemia is > 10.

In hyper K, if the TTKG is high, it means that there is high aldosterone action (appropriate), e.g. from low effective circulating volume in CHF. If TTKG is < 5, it means that aldosterone activity is low, and the reason for hyper K is due to abnormal renal handling of K, e.g. in type IV renal tubular acidosis.

In hypoK, if TTKG is still > 7, it means that there is high aldosterone activity despite the hypo K, and thus renal loss of K is the cause of the hypo K, e.g. hyperaldosteronism, Cushing’s syndrome (pseudohyperaldosteronism). If TTKG is < 5, it means that aldosterone activity is appropriately low to conserve K, and thus the hypo K is not due to renal loss, i.e. non-renal loss.

If TTKG is high with hypokalemia, look at BP.
If BP is low/normal: Look at ABG.
Low/normal BP with metabolic acidosis: RTA type I and II, diabetic ketoacidosis
Low/normal BP with metabolic alkalosis: Look at urinary chlorides.

If urinary chlorides are < 10 mEq/d: vomiting, chloridorrhea, nasogastric drainage
If urinary chlorides are > 20 mEq/d; do urinary calcium to creatinine ratio*.

* Values are expressed in mMol/L. For conversion: Creatinine 1 mg/dl = 0.080 mMol/L and calcium 1 mg/dl = 0.25 mMol/L.

If UCa/Cr ratio >0.2, consider loop diuretics or Barter’s syndrome
If UCa/Cr ratio < 0.15, consider thiazide diuretics or Gitelman’s syndrome

If TTKG is high and BP is high: do serum aldosterone level.
High BP with low aldosterone level: to do Serum cortisol level. Low cortisol level: Liddle’s syndrome; high cortisol level: Cushing’s syndrome.

If high BP with high aldosterone level; do plasma renin activity.
If renin level is high: renal artery stenosis, malignant hypertension, accelerated hypertension, juxta-glomerular apparatus tumor
If renin level is low: primary hypoaldosteronism or other problems of adrenal gland

**TREATMENT OF HYPOKALEMIA**

Although Sk is not an exact indicator of the total body K deficit, a decrease (below 4 mEq/L) of 0.27 mEq/L is approximately equivalent to 100 mEq/L of K deficit (upto a total deficit of 500 mEq/L). Sk levels of <2.0 mEq/L may reflect deficit of >1000 mEq/L.

Four factors should be taken into account for correction:

- Acid-base status: correction of coexisting metabolic acidosis without concomitant K replacement can cause the Sk to fall lower.
- Intravenous glucose administration: can cause K levels to fall: in life threatening hypokalemia, initial K replacement should be given in glucose free solutions.
- Overzealous administration of K can result in hyperkalemia.
- Coexisting hypomagnesemia prevents correction of hypokalemia.

Intravenous K is reserved for patients unable to take K orally or in severe life threatening situations, e.g. paralysis, digitalis intoxication (with arrhythmias); hypokalemia induced hepatic coma and those with ECG abnormalities.

Oral therapy is preferred because it rarely causes “overshoot” hyperkalemia, in presence of normal renal function. Oral supplement is given in doses of 20-120 mEq/day. Over the
counter salt substitutes is an economical source of K and contain 3.5-7.5 mEq/Gm (5 gm is approximately 1 teaspoon). K is available as KCl, phosphate, bicarbonate, gluconate, acetate and citrate. In general, KCl is appropriate to correct K depletion and is the only preparation effective when there is chloride depletion (metabolic alkalosis).

Oral K supplements come in a variety of liquids, powders and tablets, containing 5-40 mEq/dose. Liquid preparations are associated with gastrointestinal irritation. Enteric coated KCl tablets are associated with GI ulcerations. Intravenous K can be given safely at rates of 10mEq/hour by peripheral vein without ECG monitoring and in concentrations of up to 30mEq/L (to avoid pain/phlebitis). If Sk is <2.5 mEq/L associated with ECG abnormalities and/or severe neuromuscular complications, doses up to 40 mEq/hr can be given through a central vein with continuous ECG monitoring. Doses up to this level are rarely necessary. Frequent estimations of Sk (every 4-6 hrs) is the best guide to replacement therapy. Once indications for intravenous/emergent therapy have been resolved, less aggressive therapy should be given.

Therapeutic measures in the treatment of chronic hypokalemia include the use of oral K supplements and the K sparing diuretics spironolactone, triamterene and amiloride. Combined use of K supplements and K-sparing diuretics is contraindicated.

Following cases will exemplify how a systematic approach can resolve the issue of hypokalemia and lead to appropriate diagnosis.

Case 1:
36 yr old policeman presented with sudden onset weakness of both lower & upper limbs for 2 days, more in lower limbs & more in the morning hrs.

He was able to walk without support but had difficulty in climbing stairs & to stand from sitting position. He also felt difficulty in raising his arms overhead.

On the day of admission weakness increased & he was not able to get up from bed without support in the morning after a good sleep.

Past history: No past h/o similar illness, no h/o any chronic illness i.e. HT, DM, Thyroid disorder. No h/o fever, headache, vomiting. No h/o any drug intake

Family history: His twin brother had h/o similar symptoms, was diagnosed as hypokalemic paralysis & treated with potassium supplements but was not worked up for the etiology of hypokalemia.

In view of this history, he was diagnosed as a case of familial hypokalemic periodic paralysis.

On examination: Anxious, Pulse 104/min, regular; BP 140/80 mm of Hg, RR 24/min. Power in L/L & R/L: proximal 2/5, distal 5/5. Rest other systemic examination was unremarkable.

Patient’s motor weakness improved to normal power within hours after supplementation of K i.e. when Sk reached to normal value i.e. 4 mEq/L.

Investigations: Serum Na/K/Cl/TCO2 = 141/1.8/102/24 mEq/L,

ABG: pH 7.53, HCO3 27.8, pCO2 34, pO2 85.1, S. Creatinine 0.73mg/dl, S. Magnesium 2.3mg/dl and CPK was 1426 U/L.

Urinary K was13.7mEq/L when Sk was low, but after correction of Sk, it was 56.7mEq/L. TTKG was 6.4. Urinary chloride was 111.7mEq/L on admission. Urinary calcium/creatinine ratio was 0.516. 24 hours urinary calcium was high. Thus this was diagnosed to have Barter’s syndrome. Episodic weakness beginning after age 25 is almost never due to primary periodic paralysis. Further, low serum potassium between attacks and absence of a similar family history should raise strong suspicion of a secondary disorder.

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Case 2:

As opposed to Case 1, this was a case of 70 years female. She was diagnosed to have acute leukemia. She was admitted to ICU with pulmonary edema and received intravenous furosemide 40mg once and developed severe hypo K, leading to life threatening cardiac arrhythmias. She had difficult to treat hypo K and was referred to nephrology service. She was investigated like the above case, and was found to have high TTKG, high urinary chlorides and urine calcium/creatinine ratio of 0.12 which would go in favor of thiazide diuretics or Gitelman’s syndrome. She had never received thiazide diuretics and it was unlikely to have presentation of a hereditary defect like Gitelman’s syndrome at this age. Further investigations revealed that she had lysozymuria secondary to her leukemia which was causing hypokalemia.

The clinical features of Bartter’s syndrome (and possibly also Gitelman’s syndrome) are to a large extent caused by raised concentrations of prostaglandins. By direct action and through stimulation of natriuresis, these compounds stimulate renin secretion, thereby promoting potassium wasting. They also have a direct effect on aldosterone biosynthesis. Indomethacin has been used in both syndromes, but especially Bartter’s, for the beneficial effects of inhibiting prostaglandin synthesis.