MEDICINE

432 Team

20

Electrolytes Imbalance 2

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COLOR GUIDE: • Females' Notes • Males' Notes • Important • Additional

Objectives

1. Understand the basic physiologic principles of potassium hemostasis.
2. Know the application of physiological and clinical principles in approaching hyperkalemia.
3. Know the application of physiologic and clinical principles in approaching hypokalemia.
4. Understand the basic principles of Calcium hemostasis.
5. Know the application of physiologic and clinical principles in approaching Hypercalcaemia.

1. Potassium (K) *(normal physiology, abnormalities)*

Normal Physiology: *(sources, normal level, excretion & function)*

1. Sources and daily intake

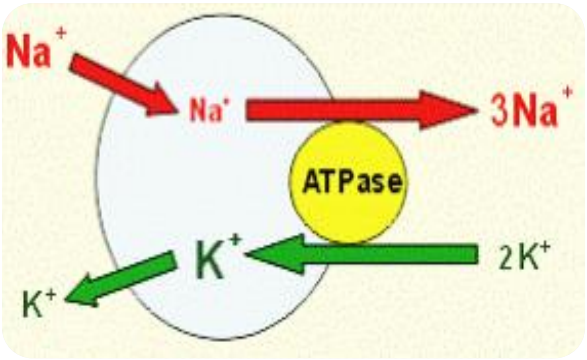
The normal daily intake vary depending on diet, average daily intake approximately 50 to 100 mmol, Oral intake is initially absorbed in the intestine and enters portal circulation.
Fruits, potatoes, beans, and grains contain more **K**, while high-fat diets usually contain low amounts of **K**

Note:

Average daily intake 50-100 is high if you consider that normal serum level is 3-5, where does it go? It either gets excreted by kidneys or pushed to the cells.

2. Normal place and level and control

- **K** is the most abundant intracellular cation (**100 - 150 mmol/L** = 98 % of total body **K**)
- What keeps the **intracellular K** concentration high: **Na/K pump**



Electrolytes should move from the higher concentration area to the lower one. The active Na/K pump pushes electrolytes **against** the gradient (it's a cell membrane pump works through energy not passively)

Enhanced by: Insulin, Beta agonists

Inhibited by: B blockers

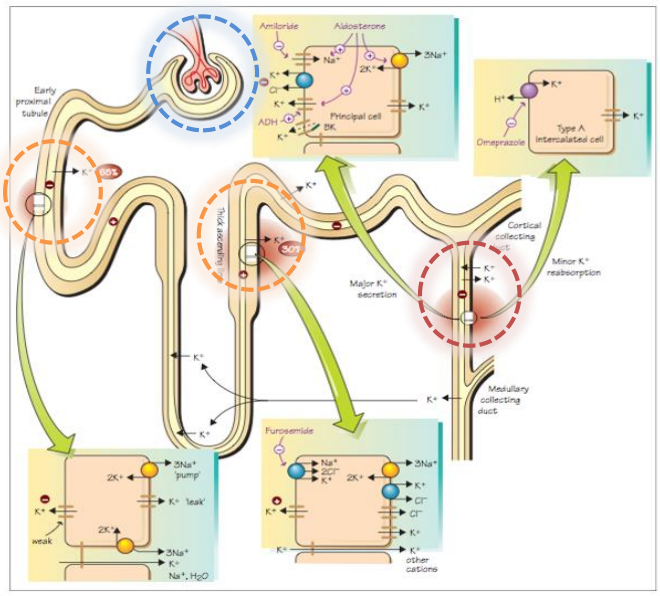
- Extracellular **K** (EC) concentration (**3.4 – 5.5 mmol/L** = 2% of total body **K** - this is actually the amount we measure in the serum).
- What keeps the **Extracellular K** concentration low**: Renal clearance,** intestinal excretion and Na/K pump. (the last one works temporarily in the first minutes while the first two are more efficient and work for 5-8 hours)
- Increased EC **K** stimulates insulin release, which in turn, facilitates **K** entry into cell by stimulating Na/K ATPase pump.
- The transient rise in serum **K** stimulates renal & intestinal clearance of extra **K**.
- Total body **K** is approximately 50 mmol/kg of body weight.

3. Excretion

There are two paths for excreting **K** out of the body:

a. **Renal clearance:** the primary and most effective mechanism, but once the **GFR** is lower than 30ml/min it is not efficient anymore.

b. **Intestinal excretion**: Only handles 10 % of the daily **K** load, still can be enhanced in case of renal failure (it is variable form one person to another)

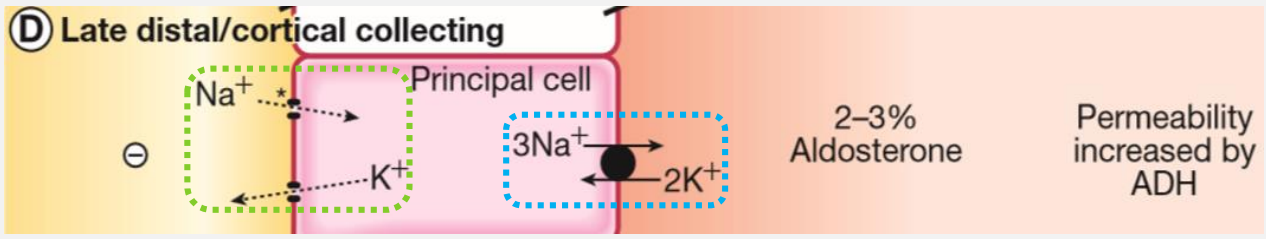


Renal clearance:

In the steady state, the kidneys excrete 90% of the daily intake of potassium. First, **K** is freely **filtered** in the **glomerulus**. 65% will be **reabsorbed** in the **proximal tubules**, while 25% of it in the **ascending loop of Henle**.

Significant **secretory** flux of potassium into the urine occurs in the **late distal tubule and cortical collecting duct**, under the effect of **aldosterone**, to ensure that the amount removed from the blood is proportional to the ingested load. Aldosterone acts on the most distal part (no further reabsorption after this process. That is why in case of high aldosterone you expect to see hypokalemia)

Davidson "Movement of **K** from blood to lumen is dependent on active (not passive) uptake across the basal cell membrane by the **active Na/K pump**, followed by **diffusion** (passive) of **K** through a luminal-membrane potassium channel into the tubular fluid. The electrochemical gradient for **K** movement into the lumen is contributed to both by the high intracellular **K** concentration and by the negative luminal potential difference relative to the blood. Factors acting on the blood side of this tubular segment include **plasma potassium** and **pH**, such that hyperkalemia and alkalosis both enhance **K** secretion directly"



Davidson "Control of body **K** balance is described as: changes in the distribution of **K** between the ICF and ECF compartments can alter plasma **K** concentration, without any overall change in total body **K** content. Potassium is driven into the cells by extracellular alkalosis and by a number of hormones, including insulin, catecholamines (through the β2 receptor) and aldosterone. Any of these factors can produce hypokalemia, whereas extracellular acidosis, lack of insulin, and insufficiency or blockade of catecholamines or aldosterone can cause hyperkalemia due to efflux of **K** from the intracellular compartment"

4. K main function

Maintains electrical gradient across cell membranes i.e. **resting membrane potential** essential for → generation of action potential (AP) essential for → intracellular metabolism e.g. protein synthesis.

Resting membrane potential depends on the balance between **Na-K**; therefore, changes in **K** concentration will affect AP, eventually altering the normal function of the cell.

Davidson" The steep concentration gradient for potassium across the cell membrane of excitable cells plays an important part in generating the resting membrane potential and allowing the propagation of the action potential that is crucial to normal functioning of nerve, muscle and cardiac tissues"

Abnormalities: *(hypo & hyper: symptoms, causes, investigations & management)*

1. Hypokalemia:

When potassium concentration <3.4

- **Symptoms:**

Muscular weakness and associated tiredness, ventricular ectopic beats or arrhythmias (lower than 2.5 you'd expect to see muscle weakness, if much lower → paralysis)

– *Davidson:* Functional bowel obstruction may occur due to paralytic ileus. Long-standing hypokalaemia causes renal tubular damage (hypokalaemic nephropathy) and interferes with the tubular response to ADH (acquired nephrogenic diabetes insipidus)

- **Causes:**

1. **Total body K is normal** (**Redistribution in cells is the only case**)

- When K gets pushed into the cells in a rate higher than normal. You will have an intracellular hyperkalemia and a serum hypokalemia, because there is no K lost from the body (total body K is normal).
  E.g. Insulin therapy, periodic paralysis. Correction of the factors - involved in K shift into the cells - may be sufficient to correct the plasma concentration.

2. **Total body K is low**

◦ **Low intake**

This is unlikely to be the only cause, except in extreme cases. E.g. malnutrition or eating disorder

◦ **Excessive loss (most common cause)**

a. **Renal loss**

- w/ hypertension: may be due to increased aldosterone secretion in (Cushing syndrome, Conn's syndrome), or a genetic defect affecting sodium channels in the distal nephron (Liddle's syndrome).

- w/o hypertension: classified according to the associated change in acid–base balance:

- Alkalosis: when diuretic use is excluded, inherited defects in tubular transport should be suspected. *(Generally, hypokalemia may cause metabolic alkalosis and vice versa – patient.co.uk)*

- Metabolic acidosis: renal tubular acidosis should be suspected *(failure of the kidney to appropriately acidify urine, it might be caused by excessive loss of bicarbonate, or insufficient secretion of hydrogen ions, anion gap is normal – Wikipedia)*

Conn's synd.: aldosterone-producing adenoma

Liddle's Synd.: also called pseudoaldosteronism, autosomal dominant disorder.

Wikipedia

Gitelman's syndrome, also known as familial hypokalaemic hypomagnesaemia, is a rare autosomal recessive hereditary salt-losing tubulopathy, (clinical features are similar to chronic treatment with furosemide) characterised by hypokalaemic metabolic alkalosis, hypomagnesaemia, and hypocalciuria, which is usually caused by mutations in the SLC12A3 gene encoding the thiazide-sensitive sodium chloride transporter

Bartter's syndrome: a group of autosomal recessive disorders with impaired salt reabsorption in the thick ascending loop of Henle with pronounced salt wasting, (clinical features are similar to chronic thiazide treatment) hypokalaemic metabolic alkalosis, and hypercalciuria

Bartter's syndrome or Gitelman's syndrome can be differentiated by:

- Hypokalaemic alkalosis with hypercalciuria (true Bartter's syndrome).
- Hypokalaemic alkalosis with hypocalciuria (Gitelman's syndrome).

b. Intestinal loss

When hypokalaemia is due to potassium wasting through the gastrointestinal tract, the cause is usually obvious clinically *(e.g. **laxative abuse** - you usually see these people with eating disorders as they don't eat to keep their body image, therapeutic abuse).*

In some cases, when there is occult induction of diarrhea or vomiting, the hypokalaemia is characteristically associated with metabolic alkalosis, *due to loss of gastric acid.* If, however, potassium loss has occurred through the surreptitious use of aperients, the hypokalaemia is generally associated with metabolic acidosis. In both cases, urinary potassium excretion is low unless there is significant extracellular volume depletion, which can raise urinary potassium levels by stimulating aldosterone production. *– Davidson*

> **Davidson: "**When there is no obvious clinical clue to which pathway is involved (renal or through GI), measurement of urinary potassium may be helpful. If the kidney is the route of potassium loss, the urine potassium is high (> 30 mmol/day). If potassium is being lost through the gastrointestinal tract, the kidney retains potassium, resulting in a lower urinary potassium (generally < 20 mmol/day).
>
> It should be noted, however, that if gastrointestinal fluid loss is also associated with hypovolaemia, activation of the renin–angiotensin–aldosterone system may occur, causing increased loss of potassium in the urine. ECG changes occur, affecting the T wave in particular.**"**

Investigations: *– Davidson*

Measurement of plasma electrolytes, bicarbonate, urine, potassium and sometimes of plasma calcium and magnesium is usually sufficient to establish the diagnosis. If the diagnosis remains unclear, plasma renin should be measured. Levels are low in patients with primary hyperaldosteronism and other forms of mineralocorticoid excess, but raised in other causes of hypokalaemia

Management:

- Stop the loss *(look at the primary etiology and stop it e.g. correction of alkalosis)*
- Replace lost K (PO or IV if rapid correction is urgently needed) PO: by mouth

(If GFR is normal, renal clearance of **K** has a huge adaptive capacity to maintain serum K level normal). **K** intake is restricted only if: *GFR is reduced, existing aldosterone axis dysfunction or insufficient Na/K pump.*

Davidso: "The rate of administration depends on the severity of hypokalemia, the presence of cardiac or neuromuscular complications. Generally, it should not exceed 10 mmol of potassium per hour. In patients with severe, life-threatening hypokalemia, the concentration of potassium in the infused fluid may be increased to 40 mmol/L if a peripheral vein is used, but higher concentrations must be infused into a large 'central' vein with continuous cardiac monitoring. In the less common situation where hypokalemia occurs in the presence of systemic acidosis, alkaline salts of potassium, such as potassium bicarbonate, can be given by mouth. If magnesium depletion is also present, replacement of magnesium may also be required for correction of hypokalemia, since low cell magnesium can enhance the mechanism for tubular potassium secretion, causing ongoing urinary losses. In some circumstances, potassium-sparing diuretics, such as amiloride, can assist in the correction of hypokalemia, hypomagnesaemia and metabolic alkalosis, especially when loop or thiazide diuretics are the underlying cause**"**

2. Hyperkalemia:

When potassium concentration >5.5

- ### Symptoms:

Sometimes there are no symptoms until cardiac arrest occurs *(In both hyper and hypo, patient is susceptible to end up with paralysis, but those with Hyper will die from arrhythmia before they reach the paralysis)*

– Davidson: The typical ECG changes: Peaking of the T wave is an early ECG sign, but widening of the QRS complex presages a dangerous cardiac arrhythmia.

- ### Causes:
  - Redistribution in cells is the only case

Redistribution of potassium from the ICF to the ECF may occur in the presence of systemic acidosis, or when the circulating levels of insulin, catecholamines and aldosterone are reduced or when the effects of these hormones are blocked

  - Massive Cell breakdown

Such as Tumor lysis syndrome *(those with malignant hematological tumors who are treated with chemo → it causes lysis of the malignant cells → a huge amount of intracellular K will be released in the circulation.)*

- Impaired Renal function

1) **Impaired GFR:** Impaired excretion of potassium associated with a reduced GFR, e.g. acute kidney injury or chronic kidney disease.

AKI can be associated with severe hyperkalemia when there is a contributing factor, such as rhabdomyolysis *(breakdown of muscle tissue that leads to the release of its contents into the blood)* or sepsis, particularly when acidosis is present.

2) **Normal GFR:** when tubular potassium secretory processes due to:

a. *Aldosterone deficiency:* Addison's disease or ACE inhibitor therapy
b. *Aldosterone resistance:* in case of inflammation of the tubulointerstitium; such as SLE; following renal transplantation and during treatment with potassium-sparing diuretics)

Davidso: "In chronic kidney disease, adaptation to moderately elevated plasma potassium levels commonly occurs → the body cannot sensate the high level → no compensation.

Acute rises in potassium triggered by excessive dietary intake, hypovolaemia or drugs may occur and destabilize the situation.

High potassium may contribute to hyperkalaemia, but is seldom the only explanation unless renal excretion mechanisms are impaired

Another cause is hyporeninaemic hypoaldosteronism where the renin–angiotensin system is inactivated. This condition typically occurs in association with diabetic nephropathy with neuropathy, and is thought to be due to impaired β-adrenergic stimulation of renin release. Other causes include angiotensin receptor antagonists, non-steroidal anti-inflammatory drugs (NSAIDs) and β-blocking drugs.

In all conditions of aldosterone deficiency or aldosterone resistance, hyperkalaemia may be associated with acid retention, giving rise to the pattern of hyperkalaemic distal *('type 4')* renal tubular acidosis"

• Investigation: *– Davidson*

Measurement of electrolytes, creatinine and bicarbonate, when combined with clinical assessment, usually provides the explanation for hyperkalaemia. In aldosterone deficiency, plasma sodium concentration is characteristically low, although this can occur in many causes of hyperkalaemia. Addison's disease should be excluded unless there is an obvious alternative diagnosis.

• Management:

- Reduce absorption: Laxatives, K chelation (Ca resonium)
- Push potassium to the cells: β agonists, insulin
- Remove extra load
- Enhance Kidney excretion: diuretics, dialysis

***Important**: Reduce Cardiac muscle irritability with Ca gluconate (only if EKG changes)*

2. Calcium (Ca) *(normal physiology, abnormalities)*

Normal Physiology: *(sources, normal level, excretion & function)*

1. Sources and daily intake

Diet: 1000 – 1500 mg /day in average

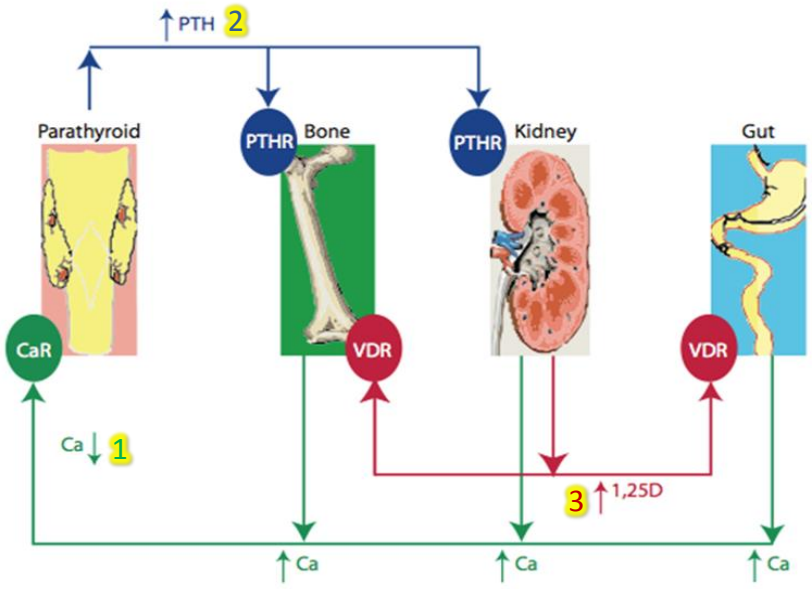
2. Normal place and level and control

- Total body Ca = 1000 g most of it (99%) is present in the **skeleton,** while non-bone calcium represents 1% of total body calcium *(distributed in the circulation and other cells)*:
  - Free ions (51%)
  - Protein-bound complexes *(albumin mainly)* (40%)
  - Ionic complexes (9%) [calcium phosphate, calcium carbonate, and calcium oxalate] *(Ionized form is the active form and the one we actually measure in the serum)*
- Calcium level is controlled by:
  - Elevators: **Parathyroid hormone (PTH), Vit D, serum Ca level** *(indirectly, by activating parathyroid gland → stimulate PTH release)*.
  - Reducers: calcitonin

PTH: elevate Ca level by enhancing bone resorption, increase renal reabsorption and by activating Vit D in the kidney.

Vit D: elevate Ca level by enhancing bone resorption and intestinal absorption.

(Check the figure below) - (Vit D: 1,25 dihydroxycholecalciferol, taken in food & synthesized in the skin)



1- Low calcium level stimulates specific receptors in parathyroid gland → releasing PTH

2- PTH enhances bone resorption + kidney reabsorption of Ca + activates Vit D in kidney.

3- Vit D increase bone resorption + Ca absorption in the gut

Net result: elevated serum Ca level

3. Excretion

- Renal excretion *-mainly-*: Ca is freely filtered in the kidney, but some of it gets reabsorbed in the tubules; depending on the serum level of Ca *(as previously mentioned; controlled by PTH)*
- Intestinal excretion

4. Ca main function *(calcium exist in our bodies in as one of two forms: boney & non-boney):*

1. ***Bone Ca:*** plays an important role in:

✓ *skeletal strength*

✓ *dynamic store* *(when body needs calcium, bone will donate, to your circulation. when body has excess Ca, the bone will store it)*

2. ***Non-Bone Ca:***

✓ *extra- and intracellular signaling*

✓ *nerve impulse transmission*

✓ *muscle contraction*

Abnormalities: *(hypo & hyper: symptoms, causes, investigations & management)*

1. Hypercalcaemia

Symptoms:

Renal: stones, nephrocalcinosis *(Ca deposits in the interstitium of the Kidney)*

Skeleton: bone pain

Gastrointestinal: nausea, vomiting, constipation, pancreatitis, peptic ulcer disease

Neuromuscular: concentration, confusion, muscle weakness

Cardiovascular: vascular calcification, short QT interval

Causes:

1. ***High PTH*** *(primary hyperparathyroidism, multiple endocrine neoplasia "MEN") or* ***high Vit D*** *(intoxication, high intake of Vit D)*
2. *High* ***intestinal absorption****: high intake of Ca, or high* ***renal reabsorption****: hyperparathyroidism and thiazide diuretics*
3. *High* ***bone resorption:*** *immobilization or Osteoclastic bone metastasis (bone lysis → Ca release in circulation)*

Investigations: – *Davidson*

If measurement of PTH levels are detectable or elevated in the presence of hypercalcaemia, then *primary hyperparathyroidism** -primary HPT- is the most likely diagnosis.

Hyperuricaemia *(high uric acid in blood)* and hyperchloraemia are suspected in patient with nephrocalcinosis and renal tubular impairment.

High plasma phosphate and alkaline phosphatase accompanied by renal impairment suggest *tertiary hyperparathyroidism**.

Patients with FHH -familial hypocalciuric hypercalcemia- *(low Ca in urine + high Ca in blood)* can present with a similar biochemical picture to primary HPT but typically have low urinary calcium excretion. Diagnosis can be confirmed by screening family members for hypercalcaemia and/or a mutation in the gene encoding the calcium-sensing receptor. If PTH is low and no other cause is apparent, then malignancy with or without bony metastases is likely. Unless the source is obvious, the patient should be screened for malignancy with a chest X-ray, myeloma screen and CT as appropriate.

**Primary HPT refers to excessive secretion of PTH due to an abnormality in the gland itself (e.g. tumor → high PTH → high Ca)*

**Secondary HPT refers to excessive secretion of PTH by the gland in response to hypocalcemia (Ca loss → low Ca → stimulate PT gland → high PTH) usually the reason of Ca loss is chronic kidney disease (chronic renal failure)*

**Tertiary HPT is a state of excessive secretion of PTH after a long period of secondary HPT, resulting in hypercalcemia. It reflects development of unregulated parathyroid function following a period of persistent parathyroid stimulation.*

2. Hypocalcemia *(included in the lecture, but not in the objectives)*

Symptoms:

Neuropsychiatric: **seizure, dementia, cataract** *(with chronic hypocalcemia),* papilledema, extrapyramidal

Neuromuscular: **paresthesia** *(with acute hypocalcemia),* **spasm, Chvostek's sign** *(for tetany),* **Trousseau's sign** *(can detect silent hypocalcemia, also called carpopedal spasm)*

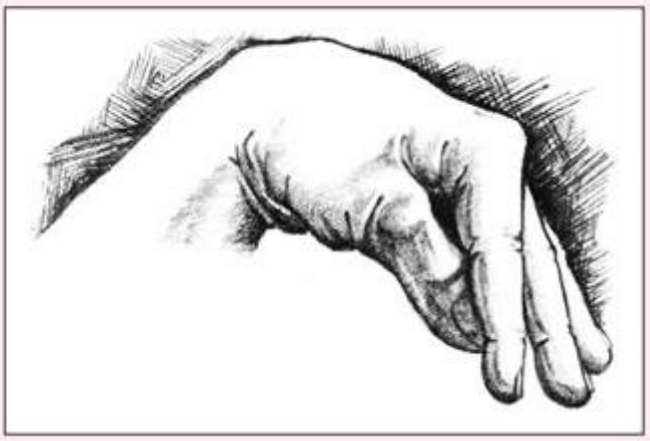
Autonomic: **biliary colic, bronchospasm** *(with acute hypocalcemia),* **diaphoresis**

Cardiovascular: **prolonged QT interval**, heart failure, hypotension

Chvostek's sign: http://www.youtube.com/watch?v=2tV4J2DxjNM

Trousseau's sign:

In the hand, carpopedal spasm involves adduction of the thumb over the palm, followed by flexion of the metacarpophalangeal joints, extension of the interphalangeal joints (fingers together), adduction of the hyperextended fingers, and flexion of the wrist and elbow joints. Similar effects occur in the joints of the feet.



Causes:

1. ***Low PTH*** *(hypoparathyroidism, postparathyroidectomy)* ***low Vit D*** *(renal failure)*
2. *defect in* ***renal reabsorption*** *(hypoparathyroidism, Loop diuretics)*
3. *defect in* ***intestinal absorption*** *(Decreased intake, malabsorption, small bowel resection, Vit D deficiency)*
4. *High* ***bone remodeling:*** *Osteoblastic bone metastasis (prostate metastasis) Hungry bone syndrome (after removing PTG, in a state of hyperparathyroidism, a sudden resorption of Ca by the bone due to sharp decrease in PTH)*

SUMMARY

1. ***Potassium:***
   - Intracellular cation, normal serum level = 4,
   - Controlled by: renal clearance, intestinal excretion, Na/K pump
   - Hypokalemia: might be caused renal loss e.g. alkalosis, intestinal loss
   - Hyperkalemia: might be caused by massive cell breakdown, impaired GFR
2. ***Calcium:***
   - Non-bone ionized calcium is the only active form
   - Controlled by: PTH, Vit D
   - Hypocalcemia: might be caused by diuretics, low PTH, intestinal e.g. small bowel resection
   - Hypercalcaemia: might be caused by hyperparathyroidism mainly

Questions

1) A 52-year-old lady with diabetes mellitus complicated by end stage kidney disease on hemodialysis is coming to the emergency department with generalized fatigue and mild shortness of breath. She has missed her dialysis session 2 days ago. Her examination revealed a pale thin lady, BP 170/90 mmHg, Temperature 37.2, raised JVP, bibasilar crackles. Labs revealed
WBC 13000 (High) Hb 8g/L (low) Creatinine 1045 mmol/L (High) K 7 mmol/L (High) ECG showed peaked T wave. What is the most important next step?

a. Request a chest X-ray
b. Start broad spectrum antibiotics
c. Calcium gluconate infusion
d. Transfuse 2 units packed red blood cells

2) Which ONE of the following drugs is known to cause hypokalemia?

a. Amlodipine.
b. Ipratropium.
c. Paracetamol.
d. Salbutamol.

432 Medicine Team Leaders

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Answers:

1st Questions: c

2nd Questions: d