Lecture 19

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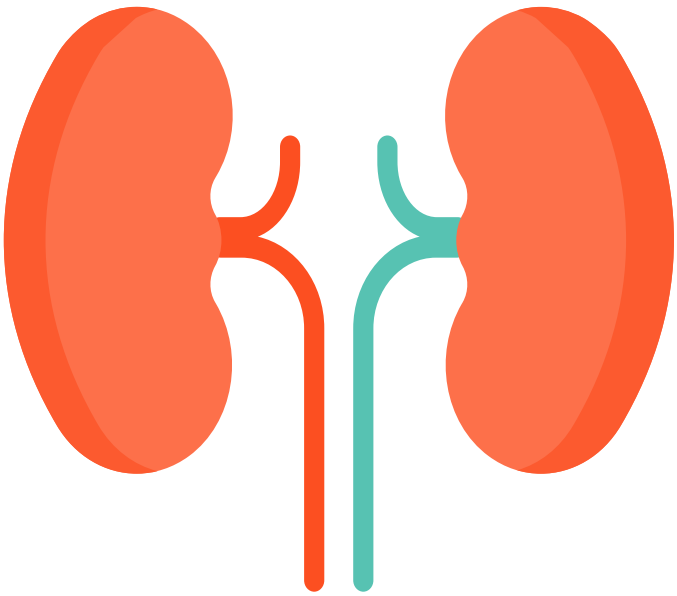

Medicine Team

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K-Ca imbalance

Objectives:

- ★ Understand the basic physiologic principles of potassium hemostasis
- ★ Know the application of physiologic and clinical principles in approaching hyperkalemia
- ★ Know the application of physiologic and clinical principles in approaching hypokalemia
- ★ Understand the basic principles of Calcium hemostasis
- ★ Know the application of physiologic and clinical principles in approaching hypercalcemia

Color index:

Original text Females slides Males slides
Doctor's notes Text book Important Golden notes Extra

Potassium

◀ Where does K come from?

- Depending on diet the normal daily intake vary, average daily intake is approximately **50 to 100 mmol.**
- Fruits, potatoes, beans, and grains, tomatos, dates
- High-fat diets usually contain low amounts of potassium.

Table 1 Potassium content of selected foods

Foods and drinks	Potassium content (mmol)
1 small banana (85 g)	8.6
Blueberries (100 g)	1.9
White mushrooms (75 g)	8.1
Broccoli, cooked (75 g)	5.8
Green beans, cooked (75 g)	3.9
Onions, cooked (75 g)	1.5
French fries (150 g)	17.7
Parboiled rice (150 g)	2.2
Spaghetti, without egg (150 g)	2.3
Orange juice (200 ml)	7.9
Milk, full fat (200 ml)	7.7
Coca Cola (200 ml)	0.1
Potato crisps (20 g)	5.1
Milk chocolate bar (20 g)	2.4
White chocolate (20 g)	1.8
Wine gums (20 g)	1.8

◀ How do we lose K?

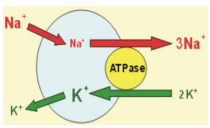
Renal clearance
Primary mechanism (90%), very efficient until GFR<30 ml/min.

intestinal excretion
Only handles 10% of the daily K^+ load
Intestinal excretion efficiency can be **enhanced in renal failure** but it is variable from one person to another

◀ Where does K live in the body?

- Total body K is approximately 50 mmol/kg body weight.
- **Intracellular (IC) K concentration** (most abundant intracellular cation)**:** (100- 150 mmol/L) ⟶ 98% of total body K.
- **Extracellular (EC) K concentration: (**3.4 – 5.5 mmol/L) ⟶ 2% of total body K[1].

◀ What keeps intracellular K^+ levels high?

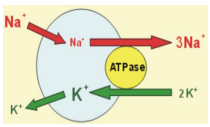


The Na/K ATPase pump.

Na/K ATPase pump is enhanced by Insulin and Beta agonists[2].

Na/K ATPase pump is inhibited by Beta blockers[3].

◀ What keeps extracellular K^+ levels low?



The Na/K ATPase pump.

Renal clearance
Requires **normal GFR**[4] and **normal Aldosterone axis**.

intestinal excretion

◀ Why is K important?

- **Maintains electrical gradient across cell membranes**, i.e. resting membrane potential[5] essential for generation of action potential.
- Essential for **intracellular metabolism** e.g protein synthesis

1: The amount we actually measure, very critical for action potential.
2: Example: **Salbutamol**.
3: as well as aspirin and digoxin.
4: the kidney does not have the ability of K^+ reabsorption, it control potassium solely through secretion (by exchanging it with Na in the distal tubules) if there is a decreased GFR, there will be less Na^+ secretion in the proximal tubule, which means less Na^+ reaching the distal convoluted tubules for K^+ exchange, leading to hyperkalemia.
5: Resting membrane potential depends on K concentration.

Potassium

◀ What happens when we eat K?

Oral [K^+] intake is initially absorbed in the intestine and enters **portal circulation**.

↓

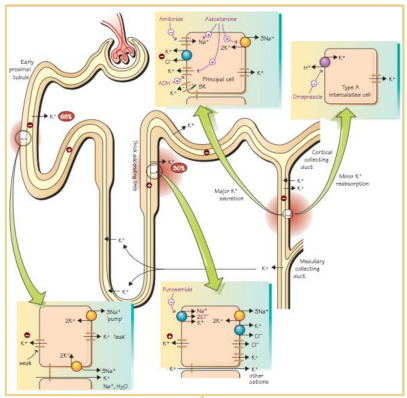
increased ECF K^+ stimulates insulin release.

↓

insulin facilitates K^+ entry into intracellular compartment by stimulating cell membrane Na^+/K^+ ATPase pump[1].

↓

The transient rise in serum K stimulates renal and intestinal clearance of extra K[2].



◀ In order to keep serum K in normal range, we need:

- Normal functioning Na/K ATPase pump.
- Intact renal response[3].

◀ What happens if K level is abnormal?

Skeletal muscle dysfunction

weakness and paralysis[4]

Arrhythmia[4]

Due to Cardiac cell irritability

◀ Can you eat too much K?

- If GFR is normal, renal clearance of K has a huge adaptive capacity.
- K intake is restricted only if:
  - ➔ GFR is reduced.
  - ➔ Existing aldosterone axis dysfunction.
  - ➔ Na/K ATPase is not efficient (blocked by drugs, Insulin ↓).

1: Preventing hyperkalemia. Hyperkalemia disturbs the electrical gradient across the cell and the resting membrane potential.
2: Stimulates renin and aldosterone release.
3: Normal GFR and aldosterone (secretion and action).
4: Hyperkalemia increases the resting membrane potential (making it less -ve).

Hypokalemia (<3.4 mmol/L)

◀ Causes:

01 ↑ Intestinal loss

- Diarrhea
- Laxatives abuse
- Villous adenoma
- Bowel obstruction/fistula
- Ureterosigmoidostomy
- Vomiting[1]
- Nasogastric aspiration

02 ↑ Renal loss

- Diuretics (loop & thiazide diuretics)
- too much aldosterone[2]
- Genetic disorders: Liddle's syndrome[3], Bartter's syndrome (similar to loop diuretics)[4]
- Gitelman's syndrome (similar to thiazide diuretics)[5]
- Renal tubular acidosis: Type 1 (distal), Type 2 (proximal)
- Acetazolamide

03 Decreased oral intake

- Malnutrition
- Eating disorders

04 Rapid transcellular shift

- Insulin therapy (esp. insulin IV infusion)
- Hypokalemic Periodic paralysis[6]
- Alkalosis[7]
- Catecholamines
- ★ **B-adrenergic agonists (e.g: salbutamol)**
- Potassium-free intravenous fluids

◀ Clinical features:

- Generally asymptomatic, but more profound hypokalemia often lead to muscular weakness and associated tiredness. Ventricular ectopic beats or more serious arrhythmias may occur and the arrhythmogenic effects of digoxin may be potentiated[8].

◀ Investigations:

01 Measurement of plasma electrolytes
bicarbonate, urine potassium and sometimes of plasma calcium and magnesium

02 If the diagnosis remains unclear
plasma renin should be measured. Levels are low in patients with primary hyperaldosteronism and other forms of mineralocorticoid excess

03 Route of K^+ loss
if the kidney is the route of potassium loss, the urine potassium is high (> 30 mmol/24 hrs), whereas if potassium is being lost through the GIT, the kidney retains potassium, resulting in a lower urinary potassium (generally < 20 mmol/24 hrs).

04 A low urine chloride (< 30 mmol/L)
characteristic of vomiting, **while a urine chloride > 40 mmol/L suggests diuretic therapy** (acute phase) or a tubular disorder such as Bartter's or Gitelman's syndrome.

◀ Treatment:

How to raise K level?

- **Stop the loss** (Treat the underlying cause)
- **IV or OP potassium:** Replace lost K with K (PO or IV if rapid correction is urgently needed).
- General rule: we advice patients with renal impairment to restrict K intake, but if they developed hypokalemia then we advice them to increase their diet intake, even those with CKD.

1: Vomiting causes **increase renal loss** of K as well, how? They will have metabolic alkalosis (every H+ you loss in vomiting introduces 1 bicarbonate molecule into the circulation by the parietal cells in the stomach), Metabolic alkalosis stimulates RAS which causes increase aldosterone release thus causing hypokalemia. Also, vomiting causes volume depletion and thus activating RAS which enhances K secretion

2: Primary hyperaldosteronism e.g. Conn's syndrome, adrenal hyperplasia or renal tumors, Cushing's syndrome, glucocorticoid excess, Excess Carbenoxelone/liquorice

3: Characterized by K^+ wasting, hypokalemia and alkalosis, but is associated with low renin and aldosterone production, and high blood pressure

4: Consists of metabolic alkalosis, hypokalemia, hypercalciuria, occasionally hypomagnesaemia, normal blood pressure, and an elevated plasma renin and aldosterone

5: Characterized by hypokalemia, metabolic alkalosis, hypocalciuria, hypomagnesaemia, normal blood pressure, and elevated plasma renin and aldosterone

6: A rare genetic disease, due to a defect in Na-K ATPase activity that increases the entry of K into the cells resulting in severe hypokalemia and paralysis.

7: Because H+ & K+ are interchangeable in the exchange mechanism, acidosis decreases and alkalosis increases the secretion of K+

8: Hypokalaemia seriously increases the risk of digoxin toxicity by increasing binding of digoxin to cardiac cells, potentiating its action, and decreasing its clearance.

Hyperkalemia (>5.5 mmol/L)

◀ Causes:

01 Na/K ATPase dysfunction:

- Beta blockers
- Digoxin
- ↓ Insulin

02 Massive cell breakdown

- Rhabdomyolysis
- Tumor lysis syndrome
- Severe hemolysis

03 Increased intake

- Dietary potassium
- Potassium-containing intravenous fluids

04 Redistribution from cells

- Acidosis
- Insulin deficiency/DKA
- Severe hypoglycemia
- B-adrenergic blockers

05 Aldosterone axis dysfunction

- Adrenal deficiency/Addison's disease
- Aldosterone resistance/Congenital adrenal hyperplasia
- ACE inhibitors & ARBs[1]
- Calcineurin inhibitors
- Spironolactone
- Eplerenone
- Heparin

06 Impaired renal function

- Acute kidney injury
- Chronic kidney disease
- NSAIDs
- B-blockers
- Tubulointerstitial disease: Interstitial nephritis, Diabetic nephropathy, Obstructive uropathy
- Amiloride

◀ Clinical features:

Progressive muscular weakness
but sometimes there are no symptoms until cardiac arrest occurs.

ECG changes

1. **Peaking of the T wave** is an early ECG sign
2. **widening of the QRS complex** presages a dangerous cardiac arrhythmia.
3. **prolonged PR interval**

◀ Investigations:

- **Measurement of electrolytes**, creatinine and bicarbonate, when **combined with clinical assessment**, usually provides the explanation for hyperkalemia. In aldosterone deficiency, plasma sodium concentration is characteristically low.

◀ Treatment:

How to lower K level?

- Reduce Cardiac muscle irritability with Ca gluconate (only if EKG changes)[2]
- ★ **Push K into cells: Insulin**[3], Beta agonists.
- Remove the K load:
- ➔ Through the kidney: diuretics (loop), dialysis (with advanced kidney disease)
- ➔ Through the gut[4]: Laxatives, K chelation (Ca resonium)

1: Reduce angiotensin II levels which may indirectly affect potassium balance by blunting the rise in aldosterone that would otherwise be provoked by hyperkalaemia
2: Ca gluconate is given for severe hyperkalemia (K>6.5) it increases the resting membrane potential which reduces the excitability of cardiac muscles.
3: Give insulin with **dextrose**, to avoid hypoglycemia
4: Lowering K through gut is very slow and take hours, so we cannot depend on it in the acute setting. In the acute setting we give insulin, B agonists, diuretics or dialysis

Calcium

◀ Where does Ca come from?

- Diet: **1000–1500 mg /day** in average.
- Total body Ca = 1000 g.
- Total plasma calcium (2.2–2.6 mmol/L)

◀ Where does Ca come from?

- The vast majority of total body calcium 99% is present in the skeleton.
- Non-bone calcium represents 1% of total body calcium.

➔ **Non-ionized form**[1]**:** Free ions (51%), protein bound complexes (40%).
➔ **Ionized form**[2]**:** Ionic complexes (9%) [calcium phosphate, calcium carbonate, and calcium oxalate]

◀ Why Ca is important?

Bone Ca

- Skeletal strength .
- Dynamic store[3].

VS

None Bone Ca

- Extra and intracellular signaling.
- Nerve impulse transmission[4].
- Muscle contraction[4].

◀ What keeps Ca in balance?

1. Total intake
2. Rate of intestinal absorption.
3. Intestinal excretion.
4. Renal reabsorption.
5. Renal excretion.
6. Bone turnover.

➔ **All these parameters are controlled by:**

1. PTH
2. Active vitamin D.
3. Serum Ionized calcium level[5].

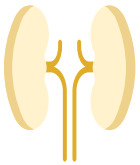
1: 91% of the non-bone Ca.
2: It's clinically important and it's the functioning Ca, the range of ionized Ca is 0.8 mmol/L. The normal range of Ca (serum) is 2.1-2.5 mmol/L.
3: Low Ca levels will increase bone resorption (↑Ca) in case of vit D deficiency or malnutrition, which leads to reduced bone density.
4: Nerve conductivity is dependent on Ca. Hypocalcemia leads to increase muscle contractility, numbness, spasm, etc..
5: Stimulates the hormones.

Calcium

◀ PTH is a hypercalcemic hormone

↑ Release of Ca form bones

bone resorption

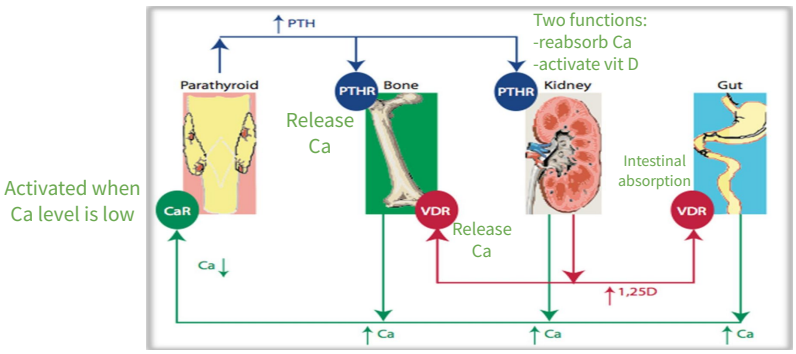


Increases renal reabsorption of Ca

Activates vitamin D in the kidney

◀ Active vitamin D is a hypercalcemic

- ↑ Intestinal absorption of Ca.
- ↑ Bone resorption.
- **Hormonal mechanisms maintain narrow physiologic range of 10%**.



◀ What can go wrong?

1. Oral intake
2. Intestinal absorption.
3. Intestinal excretion.
4. Renal reabsorption.
5. Renal excretion.
6. Bone turnover[2].

➔ **Mediated by:**

1. PTH
2. Active vitamin D.

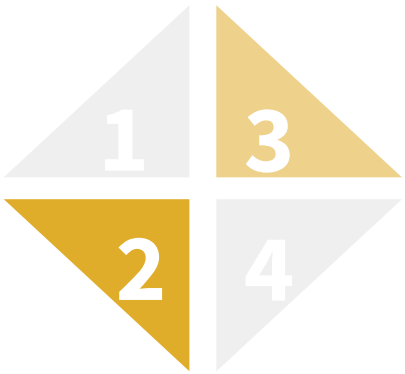
1: In the proximal part of the nephron.
2: In bone malignancy or metastasis (there's active reabsorption which will increase Ca in the blood).

Calcium

◀ Hypocalcemia

↓ Intestinal absorption
- Decreased intake.
- Malabsorption[1]
- Small bowel resection..
- Vitamin D deficiency.

↓ Renal reabsorption
- Hypoparathyroidism.
- Loop diuretics (Increase excretion of Ca)
- Tubular defects.



Bone remodeling
- Hungry bone syndrome[2]
- Patients with advanced chronic kidney disease or dialysis.

↓ PTH
- Hypoparathyroidism

↓ Vitamin D
- Renal failure

Clinical Features

It's important to know and treat the primary underlying cause

1- Cardiovascular
- **Prolonged QT interval.**
- Heart Failure.
- Hypotension.

2-Neuropsychiatry
- **Seizure** (In severe hypocalcemia)
- Dementia.
- Extrapyramidal.
- Papillodema.
- Cataract.

3-Neuromuscular
- Peripheral or perioral Paresthesia
- Spasm[3]
- **Chvostek's sign**[4]
- **Trousseau's sign**[5]

4- Autonomic
- Biliary colic.
- Bronchospasm.
- Diaphoresis.

◀ Hypercalcemia

↑ Intestinal Absorption
- Increased intake.
- Increased Vitamin D.

↑ Renal reabsorption
- Hyperparathyroidism.
- Thiazide diuretics.

↑ Bone resorption
- Osteoclastic bone metastasis. The worst
- immobilization. Mild effect

↑ PTH
- Primary Hyperparathyroidism. The worst
- Multiple endocrine neoplasia.

↑ Vitamin D (intoxication)

1: Crohn's disease, bowel resection or celiac disease.
2: Develops post parathyroidectomy. Patients with hyperparathyroidism when treated, their bones will suck all the Ca in the blood (shifting from the high bone resorption that was caused by PTH to high bone deposition), leading to severe hypocalcemia and some cases are life threatening.
3: In carpopedal spasm, the hands adopt a characteristic position with flexion of the metacarpophalangeal joints of the fingers and adduction of the thumb ('main d'accoucheur')
4: Chvostek's sign, in which tapping over the branches of the facial nerve as they emerge from the parotid gland produces twitching of the facial muscles.
5: Trousseau's sign: inflation of a sphygmomanometer cuff on the upper arm to more than the systolic blood pressure is followed by carpal spasm within 3 minutes.
6: Decrease urine Ca levels and increase blood Ca (causing hypercalcemia), that's why it's used in low doses for managing kidney stones.

◀ Hypercalcemia *(cont.)*

Clinical manifestations	
Renal "Stones"	• Nephrolithiasis. • Nephrocalcinosis[1]. • Nephrogenic Diabetes Insipidus: polyuria and polydipsia • Dehydration.
Skeleton "Bones"	• **Bone pains.** • Osteitis fibrosa cystica in hyperparathyroidism (subperiosteal resorption, bone cysts). • Arthritis. • Osteoporosis.
Gastrointestinal "Abdominal moans"	• Nausea, vomiting. • Anorexia, weight loss. • Peptic ulcer disease. • Abdominal pain • Constipation • Pancreatitis[2].
Neuromuscular "psychic groans"	• Impaired concentration and memory. • Lethargy and fatigue. • Confysuin stupor, coma. • Muscle weakness. • Corneal calcification (band keratopathy)
Cardiovascular	• Hypertension. • Cardiac arrhythmias. • ECG (shortened QT interval). • Vascular calcification.
Others	• Itching. • Keratitis, conjunctivitis

1-Deposition of Ca in the renal interstitium.
2-Sometimes the 1st presentation of hypercalcemia is pancreatitis.

Summary

Potassium Imbalance	
Basic Information	• Total body K: 50 mmol/kg body weight • Comes from our diet • Mostly intracellular (98% of total body K) and 2% is extracellular • Main importance: Maintains electrical gradient across cell membranes, i.e. resting membrane potential. • In order to maintain serum K within the normal range, we need: 1. Functional Na/K ATPase pump 2. Intact renal clearance ⇒ normal GFR & normal aldosterone axis (normal secretion & action) • K intake restricted if: 1. GFR is reduced 2. Existing aldosterone axis dysfunction 3. Na/K ATPase is not efficient (blocked by drugs or Insulin↓)
Hyperkalemia	**Causes:** 1. NA/K ATPase dysfunction 2. Massive cell breakdown 3. Impaired renal function 4. Aldosterone axis dysfunction **Clinical Features:** Arrhythmias. On ECG: tall, peaked T waves, QRS widening, PR interval prolongation, loss of P waves, and a sine-wave pattern (because hyperkalemia drops the cardiac threshold, so any action potential can stimulate it) **Treatment:** Goal ⇒ reduce K levels Reducing cardiac muscle irritability with IV Ca gluconate (membrane stabilizer) only if ECG changes. Push K into cells through: ● Insulin ● Sodium bicarbonate (if patient has acidosis) ● Beta agonists (Salbutamol 'requires high dose') Remove K load through: ● Kidney loop diuretics (furosemide) ● Gut laxatives, K chelation (Ca resonium)
Hypokalemia	**Causes:** 1. GI losses: diarrhea – laxatives 2. Renal losses: diuretics – hyperaldosteronism 3. Insufficient dietary intake: malnutrition – eating disorders 4. Rapid transcellular shift: insulin - epinephrine **Clinical Features:** Arrhythmias on ECG: prolonged normal cardiac conduction and flattening of T waves. U waves appear if severe.

Summary

Calcium Imbalance	
Basic Information	• 99% of Ca is in our skeleton (skeletal strength & dynamic store) • 1% is non-bone Ca (cell signaling, nerve impulse transmission, muscle contraction) • Ca balance is kept by: total intake, rate of intestinal absorption and excretion, renal reabsorption and excretion, and bone turnover • All parameters above are controlled by: PTH (bone & kidney) Active Vit D (bone, kidney, gut) Serum Ionized Ca levels • Hormonal mechanisms (PTH & Vit D both increase Ca) maintain narrow physiologic range of 10%
Hypercalcemia	**Causes:** 1. Increased Intestinal absorption: increased Ca/Vit D intake 2. Increased renal reabsorption: hyperparathyroidism, Thiazide diuretics 3. Increased bone resorption: osteoclastic bone metastasis, immobilization 4. High PTH: primary hyperparathyroidism, Multiple Endocrine Neoplasia 5. High Vit D: Vit D intoxication **Clinical Features:** • Cardiovascular: vascular calcification, hypertension • Neuromuscular: muscle weakness, fatigue, lethargy, impaired memory • Renal Stones: nephrocalcinosis, nephrogenic diabetes insipidus, dehydration • Bones: pain, arthritis • GIT: abdominal pain, peptic ulcer, pancreatitis, constipation, nausea, vomiting
Hypocalcemia	**Causes:** 1. Low intestinal absorption: decreased intake, malabsorption, small bowel resection, Vit D deficiency 2. Low renal absorption: hypoparathyroidism, loop diuretics, tubular defects, renal failure 3. Bone remodeling: hungry bone syndrome 4. Low PTH: hypoparathyroidism 5. Low Vit D: renal failure **Clinical Features:** • Cardiovascular: Prolonged QT interval – heart failure – hypotension • Increased neuromuscular irritability: paresthesia, spasm AKA tetany (Chvostek & Trousseau sign) • Neuropsychiatric: seizures, dementia, extrapyramidal, papilledema, cataracts

Lecture Quiz

Q1: A 65-year-old diabetic man with a creatinine of 1.6 was started on an angiotensin-converting enzyme inhibitor for hypertension and presents to the emergency room with weakness. His other medications include atorvastatin for hypercholesterolemia, metoprolol and spironolactone for congestive heart failure, insulin for diabetes, and aspirin. Laboratory studies include: K: 7.2 mEq/L Creatinine: 1.8 mg/dL Glucose: 250 mg/dL CK: 400 IU/L Which of the following is the most likely cause of hyperkalemia in this patient?

A- Worsening renal function
B- Uncontrolled diabetes
C- Statin-induced rhabdomyolysis
D- Drug-induced effect on the renin-angiotensin-aldosterone system

Q2: What is the mechanism behind using insulin in treatment of hyperkalemia?

A- Increase renal loss of K
B- Trans shift of K
C- Cell lysis
D- Help cardiac membrane from damage

Q3: Which of the following ECG changes can be found in a patient with hypocalcemia?

A- Peaked T wave
B- ST elevation
C- U wave
D- Prolonged Q-T interval

Q4: A 27-year-old alcoholic man presents with decreased appetite, mild generalized weakness, intermittent mild abdominal pain, perioral numbness, and some cramping of his hands and feet. His physical examination is initially normal. His laboratory returns with a sodium level of 140 mEq/L, potassium 4.0 mEq/L, calcium 6.9 mg/dL, albumin 3.5 g/dL, magnesium 0.7 mg/dL, and phosphorus 2.0 mg/dL. You go back to the patient and find that he has both a positive Trousseau and a positive Chvostek sign. Which of the following is the most likely cause of the hypocalcemia?

A- Poor dietary intake
B- Hypoalbuminemia
C- Pancreatitis
D- Decreased end-organ response to parathyroid hormone because of hypomagnesemia

Q5: A 21-year-old woman complains of urinary frequency, nocturia, constipation and polydipsia. Her symptoms started 2 weeks ago and prior to this she would urinate twice a day and never at night. She has also noticed general malaise and some pain in her left flank. A urine dipstick is normal. The most appropriate investigation is:

A- Serum phosphate
B- Serum calcium
C- Parathyroid hormone (PTH)
D- Plasma glucose

Answers: Q1:D | Q2:B | Q3:D | Q4:D | Q5:B |

Answers Explanation File!

THANKS!!

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Send us your feedback:
We are all ears!