Investigations for Disorders of Calcium, Phosphate and Magnesium Homeostasis

Tutorial for Specialist Portfolio Biomedical Scientists
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1. Calcium

Most abundant mineral in the human body

Funtion

- Structural – bone, teeth
- Neuromuscular – control of excitability, release of neurotransmitters, initiation of muscle contraction
- Signalling – intracellular 2nd messenger

It's effect on neuromuscular activity of particular importance in symptomatology of hypo- and hyper-calcaemia

Serum Ca

Present in 3 forms:

- Bound to protein (e.g. albumin) – pH dependent
- Complexed with citrate and phosphate
- Free ions – physiologically active – Concentration of ionised Ca maintained by homeostatic mechanisms

Very important to remember:
Labs routinely measure total Ca concentration in a serum sample. This may give rise to problems in the interpretation of results because changes in serum albumin concentration may cause changes in total Ca concentration. Therefore, **adjusted calcium** (calculation of total calcium concentration if albumin had been normal) is used to check calcium levels.

Calculation of adjusted calcium

For [Alb]<40g/L, adjusted calcium = [Ca] + 0.02 x {40-[Alb]} mmol/L

For [Alb>45g/L, adjusted calcium = [Ca] - 0.02 x {[Alb]-45} mmol/L

Homeostasis – The PTH –VitD endocrine system

Ca concentration in ECF maintained within narrow limits (ref range 2.20 – 2.60 mmol/L) by a control system involving 2 hormones and 3 organs:

Hormones

- Parathyroid hormone (PTH)

- Calcitriol or 1,25$(OH)_2$VitD

These hormones also control phosphate concentration in ECF (discuss later)

Organs
- Kidney
- Bone
- Gut

Parathyroid glands sense Ca level and secrete PTH if Ca becomes too low
PTH stimulates 1a hydroxylase enzyme activity in kidney and promotes production of calcitriol (1,25$(OH)_2$VitD), the biologically active form of Vitamin D3.
Restores Ca levels in 3 different ways:

- GI Tract : Increased intestinal absorption of dietary Ca
- Bone: Increased mobilisation of Ca from bone into the circulation
- Kidney: Increased Ca reabsorption

- <u>Hypocalceamia (abnormally low calcium)</u>

Clinical features
- Neurological (tingling, tetany, mental changes)
- Muscle cramps (changes in muscle excitability)
- Cardiac signs (abnormal ECG)
- Seizures

Clinical signs
- Trousseau's sign – BP cuff above systolic pressure and hand goes into spasm
- Chvostek's sign – Tap facial nerve in front of ear and face muscles spasm

Causes
- Commonest cause in hospital patients = Mg deficiency
- Hypoparathyroidism (Di George syndrome, surgical removal of parathyroid glands)
- CRF (chronic renal failure) – failure to activate VitD
- Vitamin D deficiency
- Artefactual (blood collected in EDTA tube)

Treatment
Treat underlying cause if possible
Give VitD supplements , Mg supplements
If tetany/seizures – IV calcium gluconate (monitor Ca levels)

- <u>Hypercalceamia (abnormally high calcium)</u>

Calcium >3.5mmol/L requires urgent treatment!!

Clinical features
Almost always present >3.5mmol/L, may be absent <3.0mmol/L

- Neurological & psychiatric (lethargy, confusion, irritability, depression)
- GI issues (anorexia, abdo pain, nausea & vomiting, constipation)
- Renal issues (polyuria, renal stones)
- Muscoskeletal issues (bone/joint pain, muscle weakness, cardiac arrhythmias)

Causes
- Commonest in hospital patients = Malignancy (cancer) but generally primary hyperparathyroidism
- Less common : Vit D intoxication (over supplementing), Familial hypocalciuric hypercalcaemia (genetic defect), Thiazide diuretics
- Uncommon: Thyrotoxicosis (increased bone turnover and release of calcium in circulation), phaeochromocytoma, immobilisation, milk-alkali syndrome (increased calcium intake and bicarbonate – self medicating)

Treatment
Depends on underlying cause:
- Malignancy – treat with bisphosphonates (inhibit bone resoption) plus IV saline to restore GFR and promote diuresis
- Primary hyperPTH – surgical removal of parathyroid adenoma followed by immediate treatment with VitD to avoid transient hypocalcaemia until parathyroids begin to operate normally

2. **Phosphate (Ref range 0.8 – 1.4 mmol/L)**

Function
- Energy – ATP/ADP
- Substrate – NADPH/NADP
- Structure – Phospholipids
- Buffers – H^+ metabolism/homeostasis

Homeostasis
Phosphate concentration is also regulated by PTH and calcitriol ($1,25(OH)_2$VitD).
- PTH promotes release from bone and decreases renal absorption
- Calcitriol promotes release from bone, increases gut reabsorption and renal absorption

- **<u>Hypophosphataemia (abnormally low phosphate)</u>**

Clinical Features
- Muscle weakness (can not generate ATP)
- Seizures
- Haemolysis, rhabdomyolysis

- Bone pain (PTH attempts to release phosphate from bone)

Causes
- VitD deficiency
- Hyperparathyroidism – increased renal loss
- GI loss
- Intracellular shift (high glucose load – glucose metabolised using ATP – phosphate drawn into cells)
- Respiratory alkalosis (activation of phosphofructokinase, phosphate is used up)

Treatment
Administration of phosphate

- <u>Hyperphosphataemia (abnormally high phosphate)</u>

Clinical Features
- Tetany and muscle weakness
- Renal bone disease (osteodystrophy)

Causes
- Renal failure (most common)
- Increased load (eg oral phosphate)
- Cellular release (rhabdomyolysis)
- Hormonal (eg hypoparathyroidism)
- Pseudo (artefactual – haemolysis)

Treatment
- Treat underlying cause
- Phosphate binders (calcium or aluminium salts) by mouth to reduce gut absorption

3. Magnesium (Ref range: 0.7 – 1.0 mmol/L)

Function
- ATP only active when Mg-ATP
- Phospholipid structure, membranes
- Several other structures eg RNA/DNA
- Cofactor for ~ 300 enzymes

- <u>Hypomagnesaemia (abnormally low magnesium)</u>

Clinical Features

Muscle weakness, tremor, delirium, positive Trousseau and Chvostek's signs, increased chance of digoxin toxicity

Causes

- Renal : renal diseases (Gitelman's syndrome), diuretics
- GI causes: reduced intake (anorexia) / reduced absorption (Coeliac disease, GI diseases)
- Redistribution (transient) : insulin, refeeding syndrome, 'hungry bone' syndrome
- Endocrine: diabetes, hyperCa, hyperaldosteronism
- Alcoholism: (very high incidence, rule our first)

Treatment

- Mild deficiency: oral supplements (this may induce diarrhoea and further Mg loss)
- Severe deficiency: IV Mg infusion

- <u>Hypermagnesaemia (abnormally high magnesium)</u>

Clinical Features
Dependent on Mg levels – paralysis of voluntary muscles, heart block/cardiac arrest

Causes

- Excess oral intake (eg antacids)
- IV (during treatment for preclampsia)
- Renal failure (chronic or acute)

Treatment
IV calcium (short-time protection against adverse effects of hypermagnesaemia)
In renal failure: dialysis

- <u>Mg as therapeutic agent</u>

- Asthma
- Eclampsia
- Dysrrhythmias