Hypercalcemia – Dr Andre Tan

Ionised calcium vs corrected calcium 00:38

- Ionised calcium is the most accurate measure
- Half of total calcium is bound to albumin/protein – calculated calcium adjusts for fluctuations in albumin/protein
- Ionised calcium indicated in critically ill patients (on CRRT, severely acidotic), multiple transfusions (high citrate content), ESRF patients on dialysis
- Ionised calcium sent in ABG syringe on ice

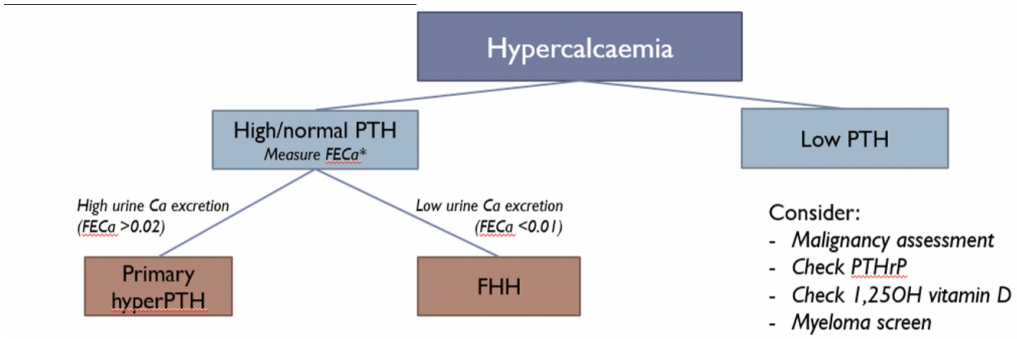
What are important points to obtain in history? 2:35

- Symptoms: Stones, bones, groans, moans, psychiatric overtones – Multiple organ systems affected

	Acute	Chronic
Gastrointestinal	Anorexia, nausea, vomiting	Dyspepsia, constipation, pancreatitis
Renal	Polyuria, polydipsia (nephrogenic DI)	Nephrolithiasis, nephrocalcinosis
Neuromuscular	Depression, confusion, stupor, coma	Weakness
Skeletal involvement	Bone pain	Osteoporosis, fractures Osteitis fibrosa cystica
Cardiac	Bradycardia, 1st deg AV block	Hypertension, digoxin sensitivity

  - Nephrogenic DI – Hypercalcemia affects aquaporin 2 production and causes nephrogenic DI, this causes patients to be dehydrated and reduces perfusion to the kidneys, which results in reduced calciuresis, causing a vicious cycle
- Drug History
  - Lithium: Affects calcium sensing receptor on parathyroid gland resulting in increased PTH secretion
  - Thiazides: Affects urinary calcium excretion; usually not a standalone cause of hypercalcemia
  - Calcium supplements
  - Chronic use of antacids
  - Vitamin D, A toxicity

What initial tests should be performed? 6:52



Fractional urinary excretion of Ca = $\frac{U_{Ca}}{S_{Ca}} \times \frac{S_{Cr}/1000}{U_{Cr}}$

- Paired PTH (fasting; intake of food can lower PTH) and calcium
- Adjuncts: Phosphate, 25OH-Vit D
  - Low phosphate either PTH or PTHrP drive process, high phosphate likely 1,25OH-Vit D driven

- If calcium is high, PTH secretion should be suppressed – hence normal or high PTH would be considered inappropriate

What and when should further tests be performed? 09:50

- Urinary calcium creatinine ratio
  - To be performed if PTH high or normal
  - Low fractional excretion of calcium in FHH
  - While 24-hour urinary collection more accurate, often times a spot urine is done for convenience – if it is low/borderline on spot urine, then can perform a 24-hour urine collection
  - Urinary studies should be performed only when calcium is high – if calcium has normalized, test is less accurate
- PTH related peptide and 1,25 hydroxy Vit D
  - Can be considered in patients with PTH independent hypercalcemia
  - May not necessarily change management/work up because of time taken for results to return
  - 1,25 hydroxy Vit D – raised in granulomatous disease, may be useful in guiding the need for steroids
  - 1,25 hydroxy Vit D and PTH related peptide – sent to mayo clinic, turnaround time of 1-2 weeks

What are the common malignancies associated with hypercalcemia? 15:47

- Humoral hypercalcaemia of malignancy (PTHrP) – 80%
  - Typically in SCC of the lung; can also occur in SCC of head and neck, breast ca, renal ca
- Direct bone destruction by lytic metastases – 20%
  - Typically in multiple myeloma
- Excess 1,25-hydroxyvit D production by lymphoma (almost all HL and 1/3 of NHL)

What is the subsequent work-up for primary hyperparathyroidism? 17:26

- Confirmation:
  - PTH-dependent hypercalcaemia
  - Urinary Ca excretion not low
- Localisation – Usually multiple modalities are performed as sensitivity and specificity of tests are not very high; looking for parathyroid adenoma/hyperplasia/rarely carcinoma
  - Parathyroid uptake scan
  - Ultrasound of the neck
  - 4D-CT neck (parathyroid protocol)
- Assessment for end-organ complications
  - XR KUB
  - BMD (hip, lumbar spine)

How do we manage primary hyperparathyroidism? 19:17

- Surgical management is the first line treatment in patient primary hyperparathyroidism when localization is definitive
- If mild asymptomatic hypercalcemia, then patients are followed up and if they meet any of the following criteria then surgery would be proposed:
  - Age < 50 years
  - Calcium > 2.8 mmol/L (more than 0.25mmol/L above ULN)
  - Skeletal
    - BMD T-score < -2.5
    - Vertebral fracture (radiologically proven)
  - Renal
    - Creatinine clearance < 60ml/min
    - 24hr urine Ca > 10mmol/day

        - § Presence of nephrolithiasis/nephrocalcinosis
- Medical Management – if patient is not fit for surgical management or not keen
    - Increased fluid intake
    - Replete vitamin D (>20ug/L) – To prevent secondary hyperparathyroidism
    - Avoid supplemental calcium
    - Cinacalcet – controls hypercalcaemia but limited benefit on bone
    - Antiresorptives for osteoporosis – may not control hyperCa

Does immobility really cause hypercalcemia? 24:22

- It is rare and it is a diagnosis of exclusion; usually requires a significant degree of immobilisation
- Mechanism: Postulated due to increased bone breakdown and turnover in the immobilised patient

How do endocrinopathies cause hypercalcemia? 26:00

- Generally rare and hypercalcemia usually mild
- Hyperthyroidism: Increased bone breakdown
- Acromegaly: Hyperparathyroidism due to associations with MEN1, rarely due to excess 1,25OH vit D
- Adrenal Insufficiency: Mechanism not known
- Pheochromocytoma: Usually related to PTHrp secretion

Familial Hypocalciuric Hypercalcemia? 27:21

- PTH and calcium usually less elevated than in primary hyperparathyroidism; also much less common than primary hyperparathyroidism
- Autosomal dominant genetic defect in calcium sensing receptor on PTH gland – resulting in a shifted set point for PTH to respond to calcium
- Usually complications minimal as extent of hypercalcemia generally mild; of note patients do not get renal stones as calcium excretion in urine is low
- Often times do not require specific treatment because of benign course
- Sometimes misdiagnosed as primary hyperparathyroidism resulting in inappropriate parathyroidectomy
- Genetic testing can be performed to confirm presence of mutation

How much IV hydration? 30:58

- Severity of hypercalcemia classified as follows: Mild < 3, moderate 3-3.5, severe > 3.5
- For mod-severe hypercalcemia, generally aim 2-6 L crystalloids over the first 24 hours (aim 1-2L in the first 1-2 hours)
- Aim urine output 100-150 ml/hour, monitor fluid status
- Monitor electrolytes – for hypoK/hypoMg
- Increased renal perfusion calciuresis

When are loop diuretics indicated? 33:31

- Loop diuretics increase tubular excretion of calcium, and also mitigates risk of fluid overload in patients who have received significant amounts of fluids – hence role of loop diuretics is usually at a later stage when patient may be approaching a fluid overload state but further calcium lowering is needed
- Dosing: Can start with IV frusemide 20mg BD then titrate to effect

Calcitonin and Anti-Resorptives 35:20

- Usually given if calcium still persistently elevated after 1-2 days of IV hydration and calcium levels remain > 3
- Calcitonin and bisphosphonates usually started together
- Calcitonin (Subcutaneous)
    - Has a fast onset but experiences tachyphylaxis after 48 hours
    - Dosing: 4 units/kg BD – Given 3-5 days

- Anti-resorptives take a longer time to act but have a longer period of action
    - Bisphosphonates
        - Can redose in 1-2 months if calcium rebounds, treat underlying cause in the interim
        - IV zolendronic:
            - Zometa (4mg) – Given for hypercalcemia
            - Aclasta (5mg) – For post menopausal osteoporosis
        - IV pamidronate: May be able to give in borderline renal function at lower dose or longer infusion: 90mg over 4 hours (Can lower to 30 or 60 mg if renal function is borderline – not EBM)
    - SC denosumab: Usually for hypercalcemia of malignancy
        - 120mg every 4 weeks

Steroids in the treatment of hypercalcemia 42:25

- Given in the context of elevated 1,25 hydroxy Vit D elevation – Granulomatous disease or lymphoma
- Steroids given as part of treatment of underlying disease

When to consider dialysis? 43:09

- Last resort measure when hypercalcemia is refractory to treatment or has other indications for dialysis

Take Home Points

- PTH is the key to evaluating etiology of hypercalcemia
- Inpatient management needed if mod-severe hypercalcemia (>3)
- Hydration is the mainstay of hypercalcemia treatment