

Information for Clinicians

Clinical Biochemistry Department

Investigation and Management of HYPERCALCAEMIA

Background

- Hypercalcaemia is commonly encountered in routine clinical practice.
- Samples for measurement of calcium should ideally be taken without a tourniquet (prolonged application of a tourniquet can result in a falsely high calcium).
- Clinical laboratories report a value for adjusted calcium by calculating an albumin-adjusted value. This is a means of trying to compensate for an abnormal concentration of albumin (in essence establishing what a patient's total calcium concentration would be if the albumin concentration was normal).
- Definitions:
 - **Mild hypercalcaemia:** (often asymptomatic): Adjusted calcium 2.6 – 3mmol/L
 - **Moderate hypercalcaemia:** Adjusted calcium 3–3.5mmol/L
 - **Severe hypercalcaemia:** Adjusted calcium >3.5mmol/L (a medical emergency)

Presentation

- Patients are often identified incidentally and are asymptomatic or can present with a variety of clinical features which may include:
 - Fatigue, muscle weakness, bony pain, depression/low mood (common)
 - Polyuria and polydipsia, kidney stones (hypercalcaemia causes a partial nephrogenic diabetes insipidus)
 - Nausea, vomiting, constipation,
 - Hypertension
 - Severe hypercalcaemia can result in confusion, coma, pancreatitis and peptic ulceration
 - Can potentiate digoxin toxicity and shorten QT interval

- **Causes**
 - 90% of cases are due to Primary Hyperparathyroidism or Malignancy (in hospital in-patients 65% is due to malignancy)

- **Primary Hyperparathyroidism (PHPT)**
 - Incidence 1-6/1000
 - More common in 5th and 6th decades
 - More common in females (Female:Male incidence 5:1)
 - Caused either by benign adenoma (approx. 80%), four gland hyperplasia (approx. 20%), parathyroid carcinoma – very rare

- **Malignancy**
 - Humoral Hypercalcaemia of malignancy (80%)
PTH related peptide mediated (PTHrp)
Lymphoma and leukaemia, Breast, Squamous cell Lung, Head & neck Squamous cell, Ovarian, Renal Cell Carcinoma

 - Lytic Bone lesions (20%)
Multiple Myeloma, Breast, Renal, Thyroid, Lung Cancers
Less likely lymphoma and leukaemia

 - 1,25 hydroxy vitamin-D production
Lymphoma especially Non Hodgkins Lymphoma

 - Ectopic PTH is rare
Ovarian, lung, thyroid papillary, rhabdomyosarcoma, pancreatic carcinoma

- **Less common**
 - Familial Hypocalcaemic Hypercalcaemia (FHH) – see below
 - Medication –Excess Vit D (ask about OTC preparations), Thiazides, Lithium, Antacids,
 - Renal Failure – Tertiary Hyperparathyroidism
 - Immobilization in Paget's Disease
 - Granulomatous disease via macrophage activation of Vitamin D (Sarcoidosis, TB)
 - Non PTH related endocrine disease - Addison's disease, Pheochromocytoma, thyrotoxicosis

- **Familial Hypocalcaemic Hypercalcaemia (FHH)**
 - This is a benign condition, which biochemically mimics primary hyperparathyroidism. It has an autosomal dominant pattern of inheritance.
 - It results from a defect in the calcium sensing receptor in the kidney and parathyroid glands.

- Patients with FHH will have a high plasma calcium, a high or normal PTH and a low urinary calcium (see below)
- Genetic testing can be undertaken in cases of suspected FHH where the results from urine investigations are equivocal (see below).

Investigation

- First sample with raised calcium
 - If cause not known send a further sample (taken without the use of a tourniquet) for calcium, vitamin D (if not already done so) and PTH (sample to arrive at laboratory in 4 hours). Review medication (e.g. thiazides may worsen hypercalcaemia).

The investigation and management of a patient with confirmed hypercalcaemia is outlined in the flowchart below. The initial key step is to interpret the PTH result in the context of the calcium

- Hypercalcaemia with appropriately suppressed PTH (<1.3pmol/L)
 - Primary hyperparathyroidism excluded. Other causes of hypercalcaemia should be sought and investigated.
- Hypercalcaemia and PTH >1.3– 2.6
 - Results are suggestive of primary hyperparathyroidism, **although other causes of hypercalcaemia should be considered**. If vitamin D deficient, replace and re-check calcium after 2 weeks. This is to detect a significant worsening of hypercalcaemia with vitamin D replacement. When vitamin D replete send an accurate 24hour urine collection for calcium and creatinine with paired plasma sample (taken on completion) also for calcium and creatinine. The laboratory will calculate the calcium clearance to creatinine clearance ratio (CCCR) from these two sets of samples and provide interpretation.
- Hypercalcaemia and PTH >2.6
 - Results are suggestive of primary hyperparathyroidism. However familial hypocalciuric hypercalcaemia (FHH) is a possible alternative diagnosis. If vitamin D deficient, replace and re-check calcium after 2 weeks. This is to detect a significant worsening of hypercalcaemia with vitamin D replacement. When vitamin D replete send an accurate 24hour urine collection for calcium and creatinine with paired plasma sample (taken on completion) for calcium and creatinine. The laboratory will calculate the calcium clearance to creatinine clearance ratio (CCCR) from these two sets of samples and provide interpretation.

- 24hr Urine Collections
 - To exclude FHH send accurate paired plasma and 24hr urine samples for calcium and creatinine. The lab will calculate a calcium clearance to creatinine clearance ratio (CCCR)
 - CCCR <0.01 in a patient with normal vitamin D status is suggestive of FHH.
 - Primary hyperparathyroidism is likely if CCCR is >0.02
 - Results between 0.01-0.02 should result in a repeat test and patients referred to endocrinology (for consideration of CaSR gene testing).

- Vitamin D
 - Please note that the laboratory assay only detects 25(OH)₂Vitamin D. Measurement of activated vitamin D 1,25(OH)₂ vitamin D is rarely needed and if considered necessary should be discussed with one of the clinical biochemists.

Instruction for patient to ensure CCCR completed correctly:

Instructions - read to the end, please seek clarification if needed:

Book a blood test appointment at your surgery - choose a day when it will be convenient for you to collect all your urine the day before.

Start the urine collection when you wake up e.g. 8am

Empty your bladder completely and flush the urine down the toilet. You will now have an empty bladder. The collection of urine will start from this point. Write the date and time on the bottle. For the rest of the day and overnight collect all urine passed into the container.

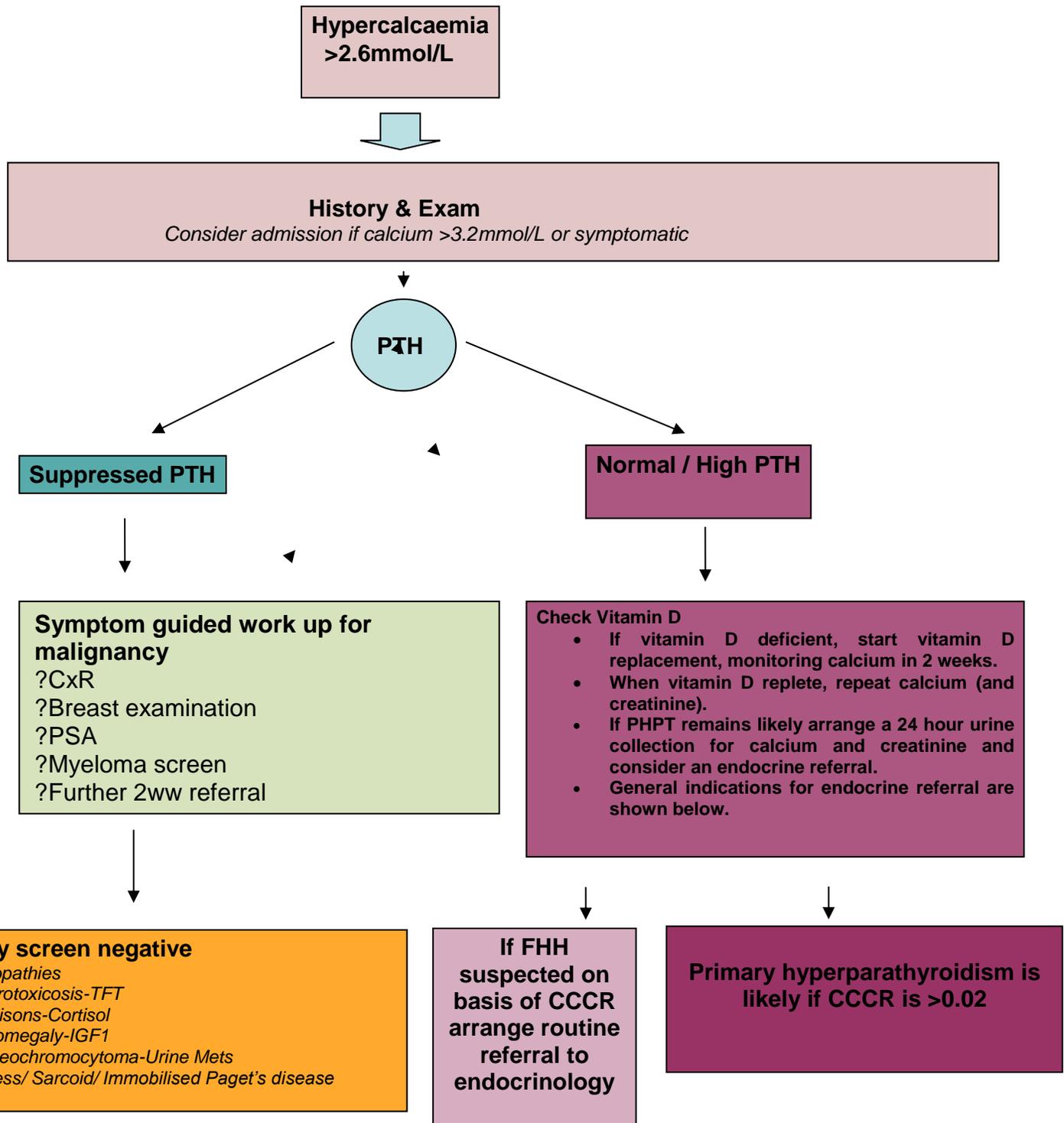
You may find it useful to collect the urine in a clean smaller container and straight away, carefully pour it into the sample container.

End of urine collection e.g. 8am, 24 hours later

After 24 hours (at the same time as the previous day) empty your bladder completely and add this urine to the container. Add no more urine. Complete the date and time. This completes the collection.

After the collection, check the cap is screwed on firmly. Fill in all details including name, date of birth and hospital number.

Return the urine container to the surgery when you go for your blood test that day. Ensure that both blood and urine are sent to the RUH with the request for 'Calcium creatinine clearance ratio'



Management

- General indications for routine referral for patients with suspected PHPT to endocrinology include the following;
 - <70 years old
 - Calcium consistently >2.8mmol/L
 - eGFR <60
 - Symptomatic (including renal stones)
 - History of osteoporosis or fracture
 - If uncertain whether referral is needed, please contact either the biochemistry or endocrine departments via Cinapsis

Reference Sources

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5. Up to date
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