Hypercalcaemia

Definition
Elevated Adjusted Calcium > 2.6 mmol/l (adjusted for albumin), taken without using a cuff.

Mild (usually no symptoms)  2.6 – 3.0 mmol/l
Moderate (start to develop symptoms)  3.0 – 3.4 mmol/l
Severe (often associated with malignancy)  > 3.4mmol/l

Symptoms and signs
Remember “Stones, bones, moans and groans”.
Fatigue, muscle weakness
Polyuria, polydipsia, kidney stones
Nausea, vomiting, constipation, pancreatitis, peptic ulcers
Depression, confusion and coma
Can potentiate digoxin and shorten QT, Hypertension

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

• Primary Hyperparathyroidism
  Incidence 1-6/1000
  50 – 60 years old
  Female:Men  5:1
  Benign adenoma 80%
  Can be part of MEN syndromes

• Malignancy
  a) Humoral Hypercalcaemia of malignancy (80%)
     PTH related peptide mediated
     Lymphoma and leukaemia, Breast, Squamous cell Lung, Head & neck
     Squamous cell, Ovarian, Renal Cell Carcinoma
  
  b) Lytic Bone lesions (20%)
     Multiple Myeloma, Breast, Renal, Thyroid, Lung Cancers  Less likely
     lymphoma and leukaemia
  
  c) 1,25 hydroxy vitamin D production
     Lymphoma especially Non Hodgkins Lymphoma
  
  d) Ectopic PTH is rare
     Ovarian, lung, thyroid papillary, rhabdomyosarcoma, pancreatic
     carcinoma
• Less common
  • Familial Hypocalciuric Hypercalcaemia (FHH)
  • Medications – Antacids, Vit D, Thiazides, Lithium
  • Renal Failure – Tertiary Hyperparathyroidism
  • Immobilization in Paget’s Disease
  • Granulomatous disease via activation of Vit D (Sarcoid, TB)
  • Non PTH related endocrine disease i.e. Addisons, Phaeo, T4

Familial Hypocalciuric Hypercalcaemia
A benign condition.
Inherited in an autosomal dominant pattern.
There is a defect in the calcium sensing receptor in the kidney and parathyroid glands.
FHH presents with high plasma calcium but low urinary calcium, with a high or normal PTH.
A spot urine calcium excretion ≤ 22 µmol/l is likely to signify FHH when hypercalcaemia is present.
Using this cut off has a sensitivity 95% and specificity 92%
As genetic testing and family studies can be undertaken now, the endocrinologists would like to see any case of suspected Familial Hypocalciuric Hypercalcaemia.

Calcium excretion index instructions

Fast the patient overnight.
In the morning obtain the SECOND voided urine.
Collect in universal container.
Request Calcium and Creatinine on urine sample.
MUST be paired with a blood sample for Calcium and Creatinine.
Hypercalcaemia > 2.6 mmol/l

History & Exam
If Ca > 3.4 mmol/l or symptomatic consider admission

PTH

Suppressed PTH
Symptom guided malignancy work up
?CXR
?Breast exam
?PSA
?Myeloma screen
?Further referral – NICE 2ww cancer guidance

Normal / High PTH

Check Vit D Must be replete before following diagnostic tree any further
Consider Urine Calcium Excretion ratio

Malignancy screen negative
Endocrinopathies
?Thyrotoxicosis-TFT
?Addisons-Cortisol
?Acromegaly-IGF1
?Phaeochromocytoma-Urine Mets
Vit D excess
Sarcoid
Immobilised Paget’s disease

LOW
Urine calcium excretion ratio

HIGH
Urine calcium excretion ratio

FHH
Routine referral to endocrinology

Hyperparathyroid Primary/tertiary
See Criteria for Endocrine Referral
Management
Refer to ://cks.nice.org.uk/hypercalcaemia for further details.

1. **Calcium > 3.4 mmol/l**. Consider admission if severe or symptomatic.

2. **Calcium < 3.4 mmol/l**
   - Review medications that may cause hypercalcaemia e.g. Thiazide diuretics, lithium, Ca/Vit D or Vit A and review fluid status.
   - Repeat to confirm and if persistent request PTH (EDTA tube) with vitamin D.

3. **PTH > 1.6 pmol/l and Calcium > 3.0 mmol/l**
   - Primary Hyperparathyroidism.
   - FAX urgent referral to Endocrinology on 0117 4148129.

4. **PTH > 1.6 pmol/l and calcium 2.61-3.0 mmol/l**
   - Probable Primary Hyperparathyroidism
   - Exclude Vitamin D deficiency
   - If Vitamin D normal follow referral criteria as below
   - If Vitamin D < 50 nmol/l then replace. Monitor calcium 2 weeks after initiating treatment.
   - Recheck PTH/Ca after 3 months and follow pathway if PTH > 1.6 pmol/l

5. **Indications for routine referral to endocrinology**
   - <70 years old
   - Calcium >2.79 mmol/l
   - eGFR 30-44 (CKD 3b)
   - Symptomatic (including renal stones)
   - History of osteoporosis or fracture

   **If referral indicated;**
   Prior to the appointment arrange a urinary calcium excretion index.

   **If referral not indicated;**
   If referral criteria are not met the patient can be managed in primary care.
   Repeat calcium in 3 months. If calcium stable, then monitor annually.
   Every 2-3 years consider a 3 site DEXA scan.
   If referral criteria met at later review - refer to endocrinology.

5. **PTH <1.6 pmol/l**
   - Non parathyroid cause. Malignancy needs to be considered.
   - If cancer suspected - 2ww referral to appropriate specialist as per NICE cancer guidelines.
   - Consider screen for Myeloma, PSA, breast exam, CXR or endocrine causes.
References

1. Clinical Knowledge summary, NHS evidence, last revised Aug 2010
2. Management Hypercalcaemia, Bilezikian, J Clin Endocrinol Metab 1993
3. Managing primary hyperparathyroidism in primary care, DTB, Mar 2010
5. Gunn and Gaffney. Annals Clinical Biochemistry. 2004
6. Up to date 2012