

BARTS ENDOCRINE E-PROTOCOLS

CALCIUM DISORDERS AND BONE

www.bartsendocrinology.co.uk

CALCIUM DISORDERS

HYPERCALCAEMIA

Clinical features to record

Symptoms: Thirst, polyuria, nocturia, tiredness, poor concentration, depression, constipation, episodes of renal colic/calculi, hypertension, family history (MEN1 or 2A, familial hypocalciuric hypercalcaemia, hyperparathyroidism jaw tumour syndrome, familial isolated hyperparathyroidism)

Examination: Signs of malignancy, sarcoidosis, corneal calcification

Investigation

- Serum calcium. This should be corrected for albumin:
 $\text{corrected Ca}^{2+} = \text{actual Ca}^{2+} + (0.02 \times (47 - \text{serum albumin}))$.
- Serum PO_4^{3-} , alkaline phosphatase.
- Determine the mechanism of hypercalcaemia by performing the investigations below.

MEASUREMENT	SCREENING FOR
FBC, ESR, chest X-ray	Sarcoidosis, malignancy, TB
Serum ACE	Sarcoidosis
U&E and urine calcium and urine creatinine	Familial benign hypercalcaemia (FBH)
Serum electrophoresis	Multiple myeloma
Serum PTH	All causes
25-hydroxyvitamin D	Interpretation of PTH level
TSH, T4, T3	Thyrotoxicosis

BARTS ENDOCRINE E-PROTOCOLS

CALCIUM DISORDERS AND BONE

www.bartsendocrinology.co.uk

PRIMARY HYPERPARATHYROIDISM

1) ESTABLISH THE BIOCHEMICAL DIAGNOSIS

This comprises elevated corrected Ca^{2+} , low PO_4^{3-} , normal alkaline phosphatase (unless bone disease present), normal or elevated serum PTH, often elevated Cl^- .

- Exclude vitamin D deficiency as cause of raised PTH.
- Exclude Familial Benign Hypercalcaemia (FBH) as cause of hypercalcaemia by calculating the ratio of calcium clearance to creatinine clearance.

Calculation of calcium clearance:

$$\frac{[\text{Urine Calcium (mmol/l)} \times \text{urine volume (ml)}]}{[\text{Plasma Calcium (mmol/l)} \times 1440]}$$

Calculation of creatinine clearance:

$$\frac{[\text{Urine Creatinine (mmol/l)} \times \text{urine volume (ml)}]}{[\text{Plasma Creatinine (mmol/l)} \times 1440]}$$

Plasma creatinine is normally expressed in $\mu\text{mol/l}$ and needs to be converted to mmol/l by dividing by 1000.

In normals and primary hyperparathyroidism, calcium clearance to creatinine clearance ratio should be > 0.01 .

The ratio can be reduced to the formula below:

$$\frac{\text{Urine Calcium (mmol/l)} \times [\text{Plasma Creatinine (}\mu\text{mol/l)} / 1000]}{\text{Plasma Calcium (mmol)} \times \text{Urine Creatinine (mmol/l)}}$$

Reference

Sopwith et al. HLA antigens and familial benign hypercalcaemia. Clinical Endocrinology 1984; 21: 57-64

2) ESTABLISH THE PHYSIOLOGICAL IMPACT OF HYPERPARATHYROIDISM

Includes assessment of:

Symptoms

Hypertension

Nephrocalcinosis (renal tract ultrasound or CT KUB)

Osteoporosis (DEXA scan)

BARTS ENDOCRINE E-PROTOCOLS

CALCIUM DISORDERS AND BONE

www.bartsendocrinology.co.uk

LOCALISATION OF PARATHYROID ADENOMA

Proceed to localisation if surgical management is proposed.

All of the techniques have limitations.

- Ultrasound of neck: The accuracy of ultrasound is highly operator dependent. It is painless, noninvasive, inexpensive and does not expose the patient to radiation. Ultrasound can identify coexistent thyroid pathology and be used to locate intrathyroidal parathyroid adenomas. However, ultrasonography neither evaluates the mediastinum nor offers functional information.
- Sesta-MIBI scanning: - The main advantage of sestamibi scans is the ability to localise parathyroid glands in ectopic sites including the mediastinum. The major factors contributing to a non-localising sestamibi study are multigland disease, small parathyroid glands, or coexistent thyroid disease.
- Selective venous sampling for PTH.
- Consider MRI of neck or CT neck (+ upper mediastinum) if no localisation or incongruity of findings.

BARTS ENDOCRINE E-PROTOCOLS

CALCIUM DISORDERS AND BONE

www.bartsendocrinology.co.uk

SELECTIVE VENOUS SAMPLING OF PARATHYROIDS

INDICATIONS

Localisation of parathyroid adenoma after ultrasound and Sesta-MIBI scanning with SPECT

PROCEDURE

Arrange admission and study in advance with interventional radiology

Blood bottles to be prepared and pre-labelled Frances Fraser ward

SITES FOR SAMPLING

Right side

1. High internal jugular
3. Low internal jugular
5. Subclavian
6. Innominate

Left side

7. High internal jugular
9. Low internal jugular
11. Subclavian
12. Innominate
14. Thymic mediastinal
15. Superior vena cava
20. High inferior vena cava
26. Low inferior vena cava
30. Right common iliac

www.bartsendocrinology.co.uk

NAME:

HOSPITAL No.:

DATE:

DIAGNOSIS:

HORMONE:

BARTS ENDOCRINE E-PROTOCOLS

CALCIUM DISORDERS AND BONE

www.bartsendocrinology.co.uk

INDICATIONS FOR SURGERY IN ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM

This is based on the 2009 guidelines from the third workshop on the management of asymptomatic primary hyperparathyroidism.

Note, in the latest guidelines, 24 hr urine calcium measurements are not an indication for surgery, as this is a poor predictor for the formation of kidney stones, is highly variable and is dependent on renal function, vitamin D status, race and sex).

However some clinicians still consider it a useful guide and the measurements are still important for the exclusion of FBH.

MEASUREMENT	
Serum calcium (>upper limit of normal)	0.25 mmol/l
Creatinine clearance (calculated)	Reduced to <60ml/min
BMD	T-score < minus 2.5 at any site and/or previous fracture fragility
Age (years)	<50

Reference

Bilezikian JP et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. JCEM 2009; 94(2):335-9.

FAMILIAL PARATHYROID SYNDROMES

10% of patients with primary hyperparathyroidism have a hereditary disorder (Hannan et al. Nature Clinical Practice Endocrinology and Metabolism 2008; 4(1):53-8)

- MEN 1 syndrome: Primary hyperparathyroidism is the first manifestation of MEN1 syndrome in over 95% of patients. Typically parathyroid hyperplasia and multigland involvement occurs. Consider genetic testing for mutations in the *MEN1* gene.
- MEN 2A syndrome: Typically parathyroid hyperplasia and multigland involvement occurs. Consider genetic testing for mutation in the *RET* gene.
- Hyperparathyroidism jaw tumour syndrome: Autosomal dominant disorder characterised by parathyroid adenomas or carcinomas, fibro-osseous tumours of the jaw, renal tumours and cysts, and uterine tumours. Consider genetic testing for mutation in the parafibromin gene
- Familial isolated hyperparathyroidism

BARTS ENDOCRINE E-PROTOCOLS

CALCIUM DISORDERS AND BONE

www.bartsendocrinology.co.uk

EMERGENCY TREATMENT OF HYPERCALCAEMIA

Severe hypercalcaemia (corrected calcium >3.5 mmol/l) remains a life-threatening acute medical emergency. Prompt treatment with hydration and adequate, frequent monitoring of serum calcium, is essential.

Hypercalcaemia induces nephrogenic diabetes insipidus which may in turn worsen dehydration and hypercalcaemia. Hypercalcaemia may also involve a significant amount of magnesium loss in the urine.

Urgent investigations

Calcium, phosphate, PTH, ESR, ALP, albumin, 25-hydroxy-Vitamin D

FBC, U and E, plasma osmolality, magnesium

Chest X-ray, ECG

Screening tests for the cause of hypercalcaemia (see above)

Management

- 1) Maintain adequate hydration. This is the cornerstone of therapy and may be all that is required. Replace the deficit and then maintain a fluid intake of 3-4 L per day. Start with iv normal saline – this may need to continue if sufficient oral intake cannot be maintained. Aim for plasma osmolality in the range 280-290 mOsm/kg. Care in patients who are elderly or in heart failure.
- 2) Bisphosphonates after rehydration. For example pamidronate 90mg in 1L of 0.9% saline infused over 4 hours. Effect is seen 24 hours after starting the infusion, with maximum effect after 5-6 days. Duration of effect may last for 14-21 days. The dose may be repeated if renal function allows.
- 3) Corticosteroids. Valuable for patients with sarcoidosis, hypervitaminosis D and many malignancies. Prednisolone 60-80mg / day if adequate hydration has not produced sufficient fall in calcium. If calcium has not fallen within 2-3 days it is unlikely to do so and the steroids should be stopped.
- 4) Mithramycin was occasionally used historically. In the event of failure of all of the above mithramycin 15 µg/kg iv in 1L of 0.9% saline over 4-6 hours may provide an improvement, beginning 8-24 hours after the infusion and persisting for several days. Repeated doses were limited by cumulative bone marrow toxicity.
- 5) Calcitonin. A dose of 100 Units sc tds may rarely be required in severe intractable hypercalcaemia.

BARTS ENDOCRINE E-PROTOCOLS

CALCIUM DISORDERS AND BONE

www.bartsendocrinology.co.uk

MANAGEMENT AFTER PARATHYROIDECTOMY

Check for symptoms of hypocalcaemia (paraesthesia, cramps etc.).

Trousseau's and Chvostek's test daily.

- Trousseau's test: Inflate blood pressure cuff to 10mmHg above the systolic pressure and maintain this pressure for up to 3 minutes. Ensure the blood pressure is maintained at the appropriate level throughout by palpation of the radial pulse. A positive test produces muscle spasm of the forearm and hand, forcing the fingers into fixed flexion at the metacarpalphalangeal joints and extension of the interphalangeal joints ('main d'accoucheur'). Note: paraesthesiae alone is not a positive test.
- Chvostek's test: Tap lightly over the facial nerve at anterior edge of masseter muscle where the parotid duct crosses the edge of the muscle. A positive test occurs when a flicking contraction of the edge of the upper lip is seen. This indicates a recent calcium fall, not necessarily to subnormal levels.

Daily U+E and corrected Ca^{2+} and magnesium

If mild symptoms and corrected $\text{Ca}^{2+} > 2.0$ mmol/l, give effervescent Ca^{2+} (Sandocal 1000; two tablets tds).

If severe symptoms and corrected $\text{Ca}^{2+} < 2.0$ mmol/l, give Ca^{2+} infusion:

Calcium infusion:

[1.7 x patient's weight in kg] ml of 10% calcium gluconate.

NB can cause tissue necrosis if extravasation so dilute in 1L N/Saline for administration or administer via central line or large patent iv access

Note: 10ml of 10% calcium gluconate contains 88mg of calcium

- If hypocalcaemia persists, continue oral Sandocal 1000 (up to 2 tablets tds might be needed) and introduce alfacalcidol – can commence at lowest dose but requirement may be 1 – 4 mcg total daily.
- Monitor PTH. If detectable, and parathyroid recovery occurs, try to wean off alfacalcidol. If PTH remains undetectable, it is likely that they will stay on alfacalcidol for life.
- Long term aim is for a low-normal calcium to minimise nephrocalcinosis and enable warning symptoms of hypocalcaemia in preference to silent hypercalcaemia.

BARTS ENDOCRINE E-PROTOCOLS

CALCIUM DISORDERS AND BONE

www.bartsendocrinology.co.uk

USE OF CINACALCET IN PRIMARY HYPERPARATHYROIDISM

INDICATIONS

Treatment of refractory primary hyperparathyroidism , after at least one failed attempt at parathyroidectomy , or in patients in whom surgery is contraindicated or who have parathyroid carcinoma

And who fulfil one or more of the following criteria:

- Overt manifestation of primary hyperparathyroidism (eg nephrolithiasis, osteitis fibrosa cystica, neuromuscular disease)
- Corrected serum calcium >3mmol/L
- PTH >6.5pmol/L
- Urine calcium >10mmol/24 hours
- Osteoporosis at any site (T score <2.5)
- Impaired renal function (creatinine clearance reduced by >30%)
- Age < 50 years

CONTRAINDICATIONS

Pregnancy or breastfeeding

Sensitivity to the drug or excipients

PRECAUTIONS

Cardiovascular disease: idiosyncratic hypotension and/or worsening of heart failure have been reported in patients with impaired cardiovascular function.

Hepatic impairment: Use with caution in patients with moderate-to-severe hepatic impairment (Child-Pugh classes B & C); cinacalcet exposure and half-life are increased; monitor closely.

Seizure disorder: Use with caution in patients with a history of seizure disorder; seizure threshold is lowered by significant serum calcium reductions. Monitor calcium levels closely.

Adverse effects may include

Gastrointestinal: Nausea (31%), vomiting (27%), diarrhoea (21%)

Neuromuscular & skeletal: Myalgia (15%)

Cardiovascular: Hypertension (7%)

Central nervous system: Dizziness (10%), seizure (1%)

Endocrine & metabolic: Testosterone decreased

Gastrointestinal: Anorexia (6%)

Neuromuscular & skeletal: Weakness (7%), chest pain (noncardiac; 6%)

BARTS ENDOCRINE E-PROTOCOLS

CALCIUM DISORDERS AND BONE

www.bartsendocrinology.co.uk

PROCEDURE

Initiate at 30mg twice daily.

Measure calcium, phosphate and urinary calcium pre-dose and 4-hours post-dose.

Measure PTH 2 weeks after initiation.

Titrate dose upwards every 2-4 weeks to control calcium, with measurements 2 weeks after adjustment.

On stable dose measure serum calcium and phosphate every 3 months and BMD by DEXA scan every year.

BARTS ENDOCRINE E-PROTOCOLS

CALCIUM DISORDERS AND BONE

www.bartsendocrinology.co.uk

HYPOPARATHYROIDISM

Biochemical Diagnosis

Hypocalcaemia, in the presence of inappropriately low or normal PTH. Exclude vitamin D deficiency.

Consider the following causes:

- Iatrogenic (post-thyroidectomy or parathyroidectomy, post radiotherapy)
- Autoimmune (either isolated or polyglandular type 1 syndrome)
- Infiltration by metastases, or systemic disease (haemochromatosis, amyloidosis, sarcoidosis, Wilson's disease, thalassaemia)
- Parathyroid agenesis (isolated or part of a complex developmental anomaly such as DiGeorge syndrome, GATA-3 mutations with sensori-neural deafness and renal anomalies)
- Reduced parathyroid hormone secretion
 - Hypomagnesaemia
 - Calcium-sensing receptor mutations
 - Parathyroid hormone gene defects
- Pseudohypoparathyroidism causing reduced PTH action

BARTS ENDOCRINE E-PROTOCOLS

CALCIUM DISORDERS AND BONE

www.bartsendocrinology.co.uk

OSTEOPOROSIS

DEXA Scanning

INDICATION

Oestrogen Deficiency

Premature ovarian failure (surgical, drug or disease induced)

Early menopause (<45 years)

Prolonged amenorrhoea (>1year)

Anorexia nervosa/bulimia

Nutritional

Malabsorption Diseases eg Coeliac, Crohn's

Chronic liver/kidney disease

Severe malnutrition

Major gastric surgery

Vitamin D or Calcium deficiencies (after checking that Vitamin D levels are normal)

Endocrine/Metabolic Disorders

Primary Hypogonadism

Cushing's

Hyperparathyroidism

Hyperprolactinaemia (secondary to oestrogen deficiency)

Strong Osteoporotic Risk Factors

Proven family history of osteoporotic fracture

High alcohol intake

Poor diet (especially low Calcium intake)

Slender build (BMI <20kg/m²)

Long-term immobility

Heavy smoking (if in conjunction with other Major risk factors)

Drug Treatments

High-dose or long-term oral corticosteroids, (>7.5mg/d or more of prednisolone or equivalent dose or another corticosteroid for 6 months or more or about to commence long-term treatment)

Chronic heparin administration especially during pregnancy.

GnRH agonists

Anti-convulsants

Other

History of multiple atraumatic/minimal trauma fracture

Radiological appearances of osteoporosis eg. previous unknown vertebral collapse

Myeloma

Known osteoporotic fracture

Marked loss of height, thoracic kyphosis (after radiological confirmation of vertebral collapse)

BARTS ENDOCRINE E-PROTOCOLS

CALCIUM DISORDERS AND BONE

www.bartsendocrinology.co.uk

PAGET's Disease

Investigations

- Alkaline phosphatase can be elevated in active disease. Serum calcium levels are usually normal.
- Radiological features on X-ray can include decrease in density of affected bones, wedge- or flame segment of bone resorption in long bones, extensive osteolytic areas in the skull (osteoporosis circumscripta), cortical thickening, increase in bone size, sclerosis, loss of corticomedullary distinction.
- Bone scintigraphy is the best method for assessing the extent of the disease.

Complications

- Deafness
- Neurological complications
- Osteogenic sarcoma

Treatment

Indications for treatment include pain, neurological complications, disease in weight bearing bones or to prevent a fracture. The mainstay of treatment is with bisphosphonates. Monitor serum alkaline phosphatase.