HYPERCALCAEMIA

Guidance for assessment in primary care

1: DEFINITIONS

Hypercalcaemia is defined as a serum adjusted calcium concentration of 2.6mmol/L or higher, on two occasions. Adjusted calcium is calcium corrected for changes in albumin concentration.

Mild hypercalcaemia	**2.60 – 2.85 mmol/L**
Moderate hypercalcaemia	**2.86 – 3.20 mmol/L**
Severe hypercalcaemia	**>3.20 mmol/L**

2: CLINICAL PRESENTATION

Presentation is usually non-specific and relates to the severity and rate of onset of hypercalcaemia. Consider hypercalcaemia if the following clinical features are present:

Gastrointestinal:	Abdominal pain Constipation Nausea and vomiting Weight loss Pancreatitis Peptic ulceration		**Renal:**	Polyuria, polydipsia, Nocturia Dehydration Nephrolithiasis Nephrocalcinosis Nephrogenic diabetes insipidus Renal failure
Musculoskeletal:	Muscle weakness and Bone pain Osteopenia / osteoporosis		**Cardiac:**	Arrhythmias Bradycardia Hypertension Shortening of the QT interval
Neurologic:	Decreased concentration Confusion and memory problems Depression, low mood Lethargy, Weakness, Stupor, coma			

3: IDENTIFY CAUSE

The 2 commonest causes of hypercalcaemia are primary hyperparathyroidism (PHP) and malignancy which, together, account for 90% of cases.

Factitious	Prolonged venous stasis through prolonged use of tourniquet. Usually results in mild hypercalcaemia
PTH mediated	**Primary hyperparathyroidism (PHP)** **Familial** hypocalciuric Hypercalcaemia (FHH) MEN syndromes
Malignancy - rapid-onset and may be severe hypercalcaemia	Lymphoma and leukaemia, Multiple Myeloma, Breast, Squamous cell Lung, Head & neck Squamous cell, Ovarian, cervix, Renal Cell Carcinoma, bladder and skin cancer, secondary bone metastases
Medications	Thiazides, Lithium, calcium carbonate (+/- calcium therapy for the prevention and treatment of osteoporosis), high dose vitamin D and Vitamin A
Chronic Renal Failure	Tertiary Hyperparathyroidism
Immobilisation	Especially in adolescence or Paget's disease when bone turnover is increased
Granulomatous disease	E.g. Sarcoidosis and tuberculosis
Non-parathyroid endocrine diseases	Thyrotoxicosis, adrenal insufficiency, phaeochromocytoma, acromegaly, vasoactive intestinal polypeptide hormone-producing tumour (VIPoma)

4: INVESTIGATION

First sample with raised calcium:

- Review medications (e.g. thiazides, lithium, Vitamin A and D, OTC/ internet purchases).
- If unknown cause, verify with a further sample (taken without the use of a tourniquet) for calcium, vitamin D (if not already done) and PTH (brown top serum sample and purple top EDTA sample required).

The PTH result must be interpreted in the context of the raised adjusted calcium results.

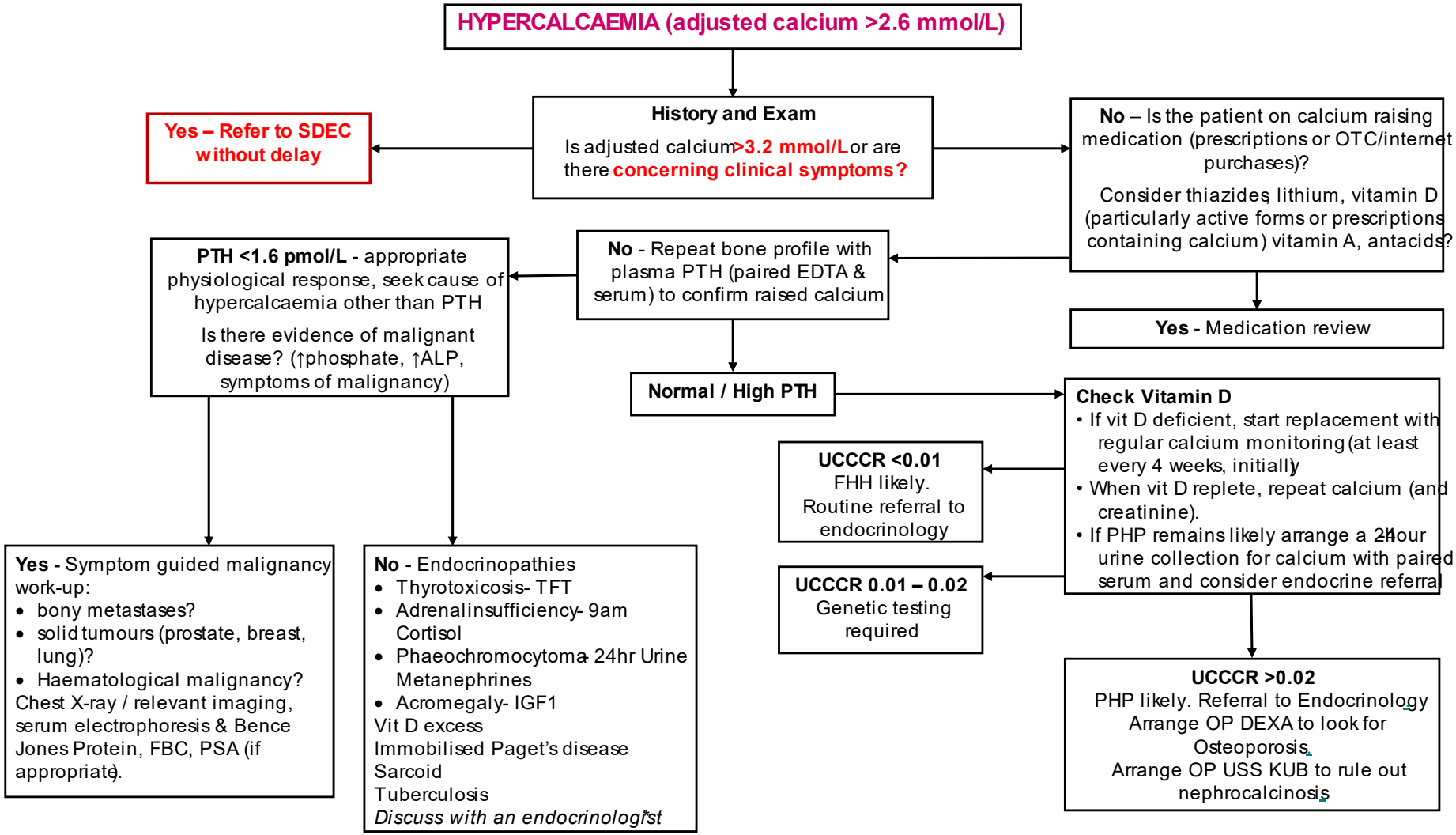
PTH <1.6 pmol/L	Appropriate physiological response, seek cause of hypercalcaemia other than PTH. If cancer suspected - 2ww referral to appropriate specialist as per NICE cancer guidelines. Consider screen for Myeloma, PSA, breast, CXR or endocrine causes.
PTH between 1.6 – 4.2 pmol/L	May be suggestive of PHP. Consider other causes of hypercalcaemia (co-existing pathology). If vitamin D deficient, replace Vitamin D (NOT Vitamin D plus Calcium). Follow local Vitamin D deficiency guidelines and **re-check calcium after 4 weeks** to detect any significant worsening of hypercalcaemia. When vitamin D replete send 24hour urine collection for calcium and creatinine with paired serum sample (taken on completion). The laboratory will calculate the calcium to creatinine clearance ratio (CCCR) and provide interpretation.
PTH >4.3 pmol/L	Results are suggestive of PHP or FHH. If vitamin D deficient, replace and re-check calcium, as above. When vitamin D replete send an accurate 24hour urine collection for calcium and creatinine with paired serum sample (taken on completion). The laboratory will calculate the CCCR and provide interpretation.

24hr Urine Collections

Familial hypocalciuric hypocalcaemia (FHH) biochemically mimics PHP. It is important to differentiate FHH from PHP as it is a benign condition that **does not need treatment**. PHP, if suspected, can be differentiated from FHH by measuring 24-hour urinary calcium excretion.

- To exclude FHH, send paired serum and 24hr urine sample for calcium and creatinine. The lab will calculate CCCR
  - CCCR <0.01 and vitamin D replete is suggestive of FHH.
  - CCCR is >0.02 and vitamin D replete is suggestive of PHP
  - Equivocal results between 0.01-0.02 should be repeated and the patient referred to endocrinology for consideration of CaSR gene testing.

Scarborough, Hull and York Pathology Service



*Please send an advice and guidance request to a member of your local endocrinology team

5: FOLLOW-UP

Referral to endocrinology should be considered when:

- Calcium consistently >2.85mmol/L
- Symptomatic (including renal stones)
- History of osteoporosis or fracture

If uncertain whether referral is needed, please send advice and guidance to either the biochemistry or endocrine departments.

6: REFERENCE SOURCES

Diagnostic approach to hypercalcemia - UpToDate – last updated 2022

Marshall, W., Day, A., Ayling, R., and Lapsley, M., 2014. Clinical Biochemistry – Metabolic and Clinical Aspects. Edinburgh: Churchill Livingstone Elsevier.

NICE [NG132] Hyperparathyroidism (primary): diagnosis, assessment and initial Management (2019)

Refer to Hypercalcaemia | Health topics A to Z | CKS | NICE for further details.