CASE SIX

Short case number: 3_17_6
Category: Endocrine & Reproductive Systems.
Discipline: Medicine
Setting: General Practice
Topic: Disorders of Calcium Metabolism

Case

Austin Solomon, 40 years old presents for follow-up of his blood test results. He has a history of recurrent renal tract calculi.

His renal function is normal. His adjusted serum calcium which is 3.20 mmol/l [2.2-2.6 mmol/L] and his serum phosphate level 0.65 mmol/L [0.7 – 1.4 mmol/L].

Questions

1. In further assessing Austin's results what key features of history and examination would you explore?
2. You consider that Austin that may have hyperparathyroidism, in reviewing the physiology of calcium metabolism outline how this would explain Austin's results.
3. Summarise the causes of hypercalcaemia and outline the further investigations [including imaging] that you would undertake to determine the cause of Austin's hypercalcaemia.
4. Develop a flow chart summarising the investigation results [including imaging] that assist in determining the likely diagnosis
5. In a table outline the types of hyperparathyroidism and the differences seen in serum calcium and PTH levels with each type.
6. Briefly outline the principles of management of hypercalcaemia.

Suggested reading:

- Kumar P, Clark ML, editors. Kumar & Clark's Clinical Medicine. 9th edition. Edinburgh: Saunders Elsevier; 2016.
- Colledge NR, Walker BR, Ralston SH, Penman ID, editors. Davidson's Principles and Practice of Medicine. 22nd edition. Edinburgh: Churchill Livingstone; 2014.

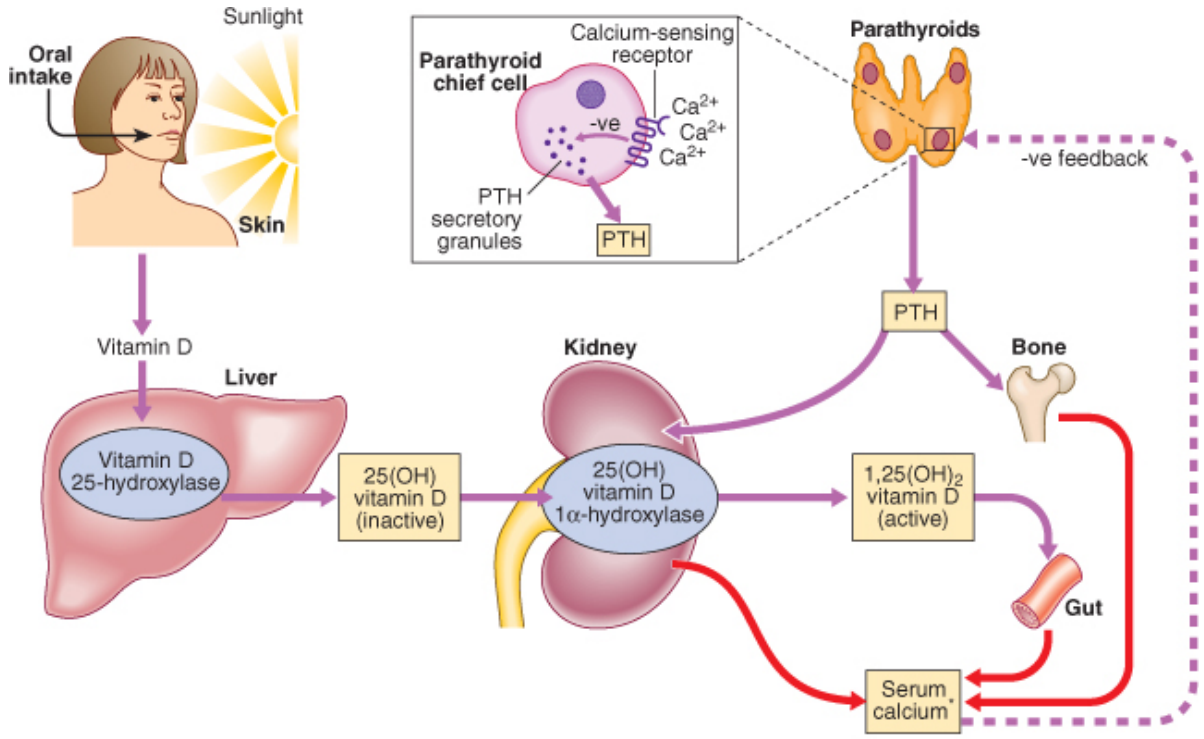
ANSWERS

1. In further assessing Austin's results what key features of history and examination would you explore?

Symptoms and signs of hypercalcaemia include polyuria and polydipsia, renal colic, lethargy, anorexia, nausea, dyspepsia and peptic ulceration, constipation, depression, drowsiness and impaired cognition. Patients with malignant hypercalcaemia can have a rapid onset of symptoms and may have clinical features that help to localise the tumour.

Patients with primary hyperparathyroidism may have a chronic, non-specific history. Their symptoms are described by the adage 'bones, stones and abdominal groans'. However, about 50% of patients with primary hyperparathyroidism are asymptomatic. In others, symptoms may go unrecognised until patients present with renal calculi (5% of first stone formers and 15% of recurrent stone formers have primary hyperparathyroidism). Hypertension is common in hyperparathyroidism. Parathyroid tumours are almost never palpable. A family history of hypercalcaemia raises the possibility of FHH or MEN

2. You consider that Austin that may have hyperparathyroidism, in reviewing the physiology of calcium metabolism outline how this would explain Austin's results.



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3. Summarise the causes of hypercalcaemia and outline the further investigations [including imaging] that you would undertake to determine the cause of Austin's hypercalcaemia.

CAUSES OF HYPERCALCAEMIA

With normal or elevated (i.e. inappropriate) PTH levels
• Primary or tertiary hyperparathyroidism • Lithium-induced hyperparathyroidism • Familial hypocalciuric hypercalcaemia
With low (i.e. suppressed) PTH levels
• Malignancy (e.g. lung, breast, renal, ovarian, colonic and thyroid carcinoma, lymphoma, multiple myeloma) • Elevated 1,25$(OH)_2$ vitamin D (e.g. vitamin D intoxication, sarcoidosis, HIV) • Thyrotoxicosis • Paget's disease with immobilisation • Milk-alkali syndrome • Thiazide diuretics • Glucocorticoid deficiency

Investigations

The PTH is low b/c even though ↑PTH causes increased bone resorption, it also stimulates the kidneys to excrete a lot of Ca.

Low plasma phosphate and elevated alkaline phosphatase support a diagnosis of primary hyperparathyroidism or malignancy. High plasma phosphate and alkaline phosphatase accompanied by renal impairment suggest tertiary hyperparathyroidism. Hypercalcaemia may cause nephrocalcinosis and renal tubular impairment resulting in hyperuricaemia and hyperchloraemia.

The most discriminant investigation is the measurement of PTH using a specific immunoradiometric assay. If PTH is normal or elevated and urinary calcium is elevated, then hyperparathyroidism is confirmed. Low urine calcium excretion indicates likely FHH and this can often be confirmed by screening family members for hypercalcaemia. Genetic analysis of the calcium-sensing receptor is also possible.

If PTH is low and no other cause is apparent, then malignancy with or without bony metastases is likely. PTH-related peptide, which is often responsible for the hypercalcaemia associated with malignancy, is not detected by modern PTH assays, but can be measured by a specific assay (although this is not usually necessary). Unless the source is obvious, the patient should be screened for malignancy with a chest X-ray, isotope bone scan, myeloma screen, serum angiotensin-converting enzyme (elevated in sarcoidosis), and further imaging as appropriate.

4. Develop a flow chart summarising the investigation results [including imaging] that assist in determining the likely diagnosis

   See above

5. In a table outline the types of hyperparathyroidism and the differences seen in serum calcium and PTH levels with each type.

Type	Serum calcium	PTH
Primary	Raised	Not suppressed
Single adenoma (90%) Multiple adenomas (4%) Nodular hyperplasia (5%) Carcinoma (1%)		
Secondary	Low	Raised
Chronic renal failure Malabsorption Osteomalacia and rickets		
Tertiary	Raised	Not suppressed

6. Briefly outline the principles of management of hypercalcaemia.

TREATMENT OF SEVERE HYPERCALCAEMIA

Rehydration with normal saline
• To replace as much as a 4-6 l deficit • May need monitoring with central venous pressure in old age or renal impairment
Bisphosphonates, e.g. disodium pamidronate 90 mg i.v. over 4 hours
• Causes a fall in calcium which is maximal at 2-3 days and lasts a few weeks • Unless the cause is removed, follow up with an oral bisphosphonate
Additional rapid therapy may be required in very ill patients
• Forced diuresis with saline and furosemide • Glucocorticoids, e.g. prednisolone 40 mg daily • Calcitonin • Haemodialysis
Treat the cause

Hypercalcaemia in patients with primary hyperparathyroidism responds less well to glucocorticoids and bisphosphonates than in those with malignancy. Urgent neck surgery is occasionally required, but strenuous attempts should be made to replace fluid deficits and lower the serum calcium concentration before administering an anaesthetic.

Most patients do not require urgent treatment. Currently, the only long-term therapy is surgery, with excision of a solitary parathyroid adenoma or debulking of hyperplastic glands.

The selection of patients with primary hyperparathyroidism who require surgery is not always straightforward. Surgery is indicated for young patients (< 50 years) and those with clear-cut symptoms or documented complications such as peptic ulceration, renal stones, renal impairment or osteopenia. However, a large number of patients have only vague symptoms or are asymptomatic. They can be reviewed every 6-12 months, with assessment of symptoms, renal function, serum calcium and bone mineral density. They should be encouraged to maintain a high oral fluid intake to avoid renal stones.