QUESTION 69

A 54yo Indian woman complains of a constant pain in her hips which is worse on standing and walking. She has mild weakness of hip flexion and walks with difficulty. She is a vegetarian and avoids dairy products. She immigrated to New Zealand three years ago. A pelvic X-ray is normal. The following blood tests are obtained:

- Alkaline phosphatase (ALP) 457U/L [30-115]
- Corrected calcium 2.13mmol/L [2.15-2.57]
- Phosphate 0.79mmol/L [0.90-1.55]
- PTH 16.0pmol/L [1.3-7.6]

The most appropriate next investigation is:

A. Dual-energy X-ray absorptiometry (DEXA) scan
B. Bone biopsy
C. Isotope bone scan
D. Vitamin D levels
E. 24-hour urinary calcium

This woman has secondary hyperparathyroidism due to hypocalcaemia. Also note that her phosphate level is low. This picture could be seen in pseudohypoparathyroidism or in vitamin D abnormalities. Elevated ALP and the musculoskeletal pain fits with osteomalacia due to vitamin D deficiency. This is also more likely given the dietary history (vitamin D largely from dairy and fish) and the move from a warm environment to a cool environment (UTD specifically mentioned Indian immigrants in this situation – don’t get enough sunlight).

The correct answer is D.

DEXA seems to be used for the diagnosis of osteoporosis but not much for osteomalacia. A bone biopsy is the gold standard for osteomalacia but it is rarely used any more. Usually the diagnosis can be made on clinical features and bloods. A bone scan may be useful if there is concern of osteoblastic bone mets. This would not be an initial investigation though. 24 hour urinary calcium is not going to be helpful as renal losses of calcium alone do not cause hypocalcaemia (see below).

HYPOCALCAEMIA

CAUSES:

1) Hypoparathyroidism
   a. Surgical resection
   b. Idiopathic
   c. Infiltration
   d. HIV infection
   e. Pseudohypoparathyroidism
2) Vitamin D deficiency
   a. Including chronic renal failure

3) Extracellular deposition/intravascular binding of calcium
   a. Hyperphosphataemia
   b. Acute pancreatitis
   c. Osteoblastic bone mets
   d. Intravascular complexing with citrate, lactate, forscarnet or EDTA
   e. Acute respiratory alkalosis

4) Disorder of magnesium metabolism

5) Others
   a. Sepsis
   b. AD hypocalcaemia
   c. Fluoride intoxication
   d. Drugs

HYPOPARATHYROIDISM

Low parathyroid hormone levels mean that calcium reabsorption from the kidneys, intestinal calcium absorption and calcium release from bone are not increased in response to low serum calcium levels.
- Characterised by end-organ resistance to the effects of PTH
- Normally PTH binds to the PTH receptor, which activates cAMP through guanine nucleotide regulator proteins (Gs). These proteins consist of alpha, beta and gamma subunits
- Pseudohypoparathyroidism is classified into type I and II, type I further subdivided into Ia, Ib and Ic

- Ia: Decreased Gs-alpha protein
  o Hypocalcaemia, hyperphosphataemia, normal or high PTH, low calcitriol, vitamin D may be low due to suppression by hyperphosphataemia and decreased PTH stimulation
  o Can also affect other endocrine systems – resistance to TSH, gonadotropins, glucagon
  o Albright’s hereditary osteodystrophy (features include round face, short stature, short 4th MC)
- Ib: Resistance to PTH with abnormal cAMP response to PTH (likely due to receptor abnormality)
- Ic: Resistance to multiple hormonal receptors but normal Gs-alpha protein expression
- II: PTH raises cAMP normally but fails to increase levels of serum calcium or urinary phosphate excretion
  o Hypocalcaemia, hypophosphaturia, elevated PTH
  o First need to rule out vitamin D deficiency

VITAMIN D DEFICIENCY
Vitamin D deficiency leads to impaired calcium absorption from the gut. Hypocalcaemia results in secondary hyperparathyroidism which causes calcium release from bone and reabsorption of calcium in the kidneys. PTH can maintain normal serum calcium levels for a time but vitamin D deficiency leads to resistance to PTH in bone and renal tubules -> hypocalcaemia. PTH then causes only mild increase in serum calcium. PTH also has the effect of promoting phosphaturia → hypophosphataemia which exacerbates demineralisation of bone. Combined effect of lower Ca2+ and low PO4 leads to loss of bone mineralisation and if prolonged, osteomalacia. Non-specific musculoskeletal pain is common. ALP often elevated due to PTH-mediated bone turnover. Because PTH stimulates 1-alpha hydroxylase, there is increased synthesis of 1,25(OH)2 vitamin D despite a deficiency of 25(OH)D so make sure the correct form of vitamin D is measured.
Causes:

1) Deficient Intake/Absorption
   a. Dietary deficiency
   b. Inadequate sunlight exposure
   c. Malabsorption (Gastrectomy, Small bowel disease)
   d. Pancreatic insufficiency

2) Defective 25-hydroxylation
   a. Biliary cirrhosis
   b. Alcoholic cirrhosis
   c. Anticonvulsants

3) Defective 1-alpha 25-hydroxylation
   a. Hypoparathyroidism
   b. Renal failure (CRF also leads to impaired PO4 excretion)
   c. Vitamin D-dependent rickets type 1 – mutation in 1-alpha hydroxylase → osteomalacia, hypocalcaemia, secondary hyperparathyroidism, markedly decreased 1,25 (OH)2 vitamin D, no alopecia

4) Defective Target Organ Response to Calcitriol
   a. Vitamin D-dependent rickets type 2 – osteomalacia, hypocalcaemia, secondary hyperparathyroidism, normal 25 vitamin D, markedly increased 1,25(OH)2 vitamin D, alopecia

MAGNESIUM ABNORMALITIES

- Hypomagnesemia causes
  o PTH resistance
  o Decreased PTH secretion
- Severe hypermagnesemia (Mg >5)
  o Rare
  o Suppresses PTH

EXTRACELLULAR DEPOSITION

- Acute hyperphosphataemia causes calcium deposition in bone and extraskeletal tissue
- Chronic hyperphosphataemia (usually due to CRF) inhibits calcium efflux from bone and reduces calcium absorption due to reduced renal synthesis of vitamin D
- Acute pancreatitis causes precipitation of calcium soaps in the abdomen
- Osteoblastic metastases can sometimes cause hypocalcaemia, presumably due to deposition of calcium within the mets
- Hungry bone syndrome occurs in patients with primary hyperparathyroidism who undergo parathyroidectomy – leads to deposition of calcium in bone

INTRAVASCULAR BINDING

- Citrate, lactate and foscarnet chelate calcium in serum
- Acute respiratory alkalosis increases calcium binding to albumin and also reduces ionised calcium concentration
HYPERCALCIURIA

- Can lead to a negative calcium balance but not hypocalcaemia due to the compensatory mechanisms of PTH

DRUGS

- Agents that inhibit bone resorption
  o Calcitonin
  o Bisphosphonates
  o Oestrogens
- Chemotherapy agents
  o Cisplatin
  o Cytosine arabinoside
  o Doxorubicin
- Antimicrobials
  o Ketoconazole
  o Foscarnet
  o Pentamidine
- Diuretics
  o Frusemide
- Cinacalcet

INVESTIGATION OF HYPOCALCAEMIA

- Serum albumin
  i. To exclude factitious hypocalcaemia
- Serum ionised calcium
- Magnesium
- Serum phosphate
  i. High PO4 in healthy kidneys is due to hypoparathyroidism or pseudohypoparathyroidism
  ii. High PO4 and PTH occurs in renal failure – impaired PO4 excretion
  iii. Low PO4 indicates either excess PTH secretion (secondary hyperparathyroidism) or low dietary phosphate intake
- PTH
  i. Low in hypoparathyroidism
  ii. PTH elevated in pseudohypoparathyroidism and abnormalities of vitamin D metabolism
  iii. PTH can be high or low in hypomagnesemia
- Vitamin D
- ALP
  i. In PTH deficiencies, ALP normal or slightly low
  ii. Elevated in osteomalacia and rickets
- Skeletal XRs
  i. Look for osteomalacia, rickets and osteoblastic metastases
- Bone biopsy
  i. Can confirm the diagnosis of osteomalacia