BONE DISEASE

The finding that a patient has hypercalcaemia or hypocalcaemia does not imply that there will be marked bone changes. Conversely, severe bone disease can occur whilst serum calcium levels appear quite normal. The main bone diseases are:

- osteoporosis
- osteomalacia and rickets
- Paget's disease.

BONE METABOLISM

Bone is constantly being broken down and reformed in the process of bone remodelling (Fig. 1). The clinician looking after patients with bone disease will certainly need to know to what extent bone is being broken down, and, indeed, if new bone is being made. Biochemical markers of bone resorption and bone formation can be useful in assessing the extent of disease, as well as monitoring treatment.

Hydroxyproline, from the breakdown of collagen, can be used to monitor bone resorption. However, urinary hydroxyproline is markedly influenced by dietary gelatin. Better markers of resorption are required. One candidate would seem to be another collagen degradation product: the fragments of the molecule containing the pyridinium cross links. Deoxypyridinoline is one such crosslink which is specific for bone, and not metabolized or influenced by diet.

The activity of the enzyme alkaline phosphatase has traditionally been used as an indicator of bone turnover. The osteoblasts which lay down the collagen framework and the mineral matrix of bone have high activity of this enzyme. Increased osteoblastic activity is seen as an elevated alkaline phosphatase activity in a serum specimen. Indeed, children who have active bone growth compared with adults have higher 'normal' alkaline phosphatase activity in serum. However alkaline phosphatase is also produced by the cells lining the bile canaliculi and is a marker for cholestasis. The bone isoenzyme of alkaline phosphatase may be measured, but there is need for a more specific and more sensitive marker.

Osteocalcin meets some of these requirements. It is made by osteoblasts and is an important noncollagenous constituent of bone. Not all of the osteocalcin which an osteoblast makes is incorporated into the bone matrix. Some is released into plasma, and provides a sensitive indicator of osteoblast activity. The test is available in specialized laboratories.

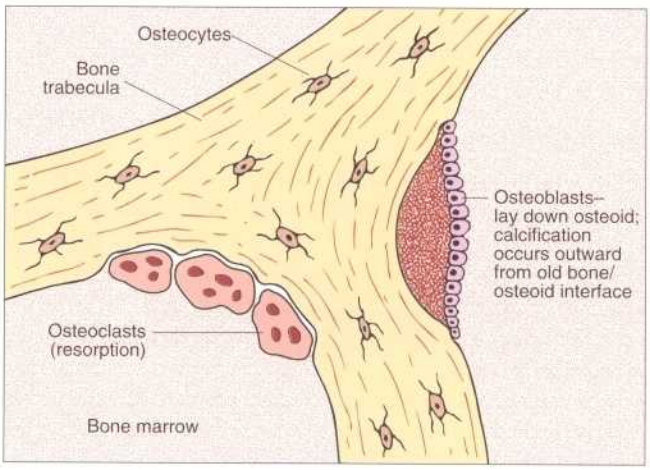

Fig. 1 **Bone remodelling.**

COMMON BONE DISORDERS

Osteoporosis

Osteoporosis is the commonest of bone disorders and is discussed separately on page 72.

Osteomalacia and rickets

Osteomalacia is the name given to defective bone mineralization in adults (Fig. 2). Rickets is characterized by defects of bone and cartilage mineralization in children. Vitamin D deficiency was once the most common reason for rickets and osteomalacia, but the addition of vitamin D to foodstuffs has almost eliminated the condition except in the elderly or housebound, the institutionalized, and in certain ethnic groups. Elderly Asian women with a predominantly vegetarian diet are particularly at risk. Vitamin D status can be assessed by measurement of the main circulating metabolite, 25-hydroxycholecalciferol, in a serum specimen. The metabolism of vitamin D is shown in Figure 3.

In severe osteomalacia due to vitamin D deficiency, serum calcium will fall, and there will be an appropriate increase in PTH secretion. Serum alkaline phosphatase activity will also be elevated.

The bony features of osteomalacia and rickets are also shared by other bone diseases (see later).

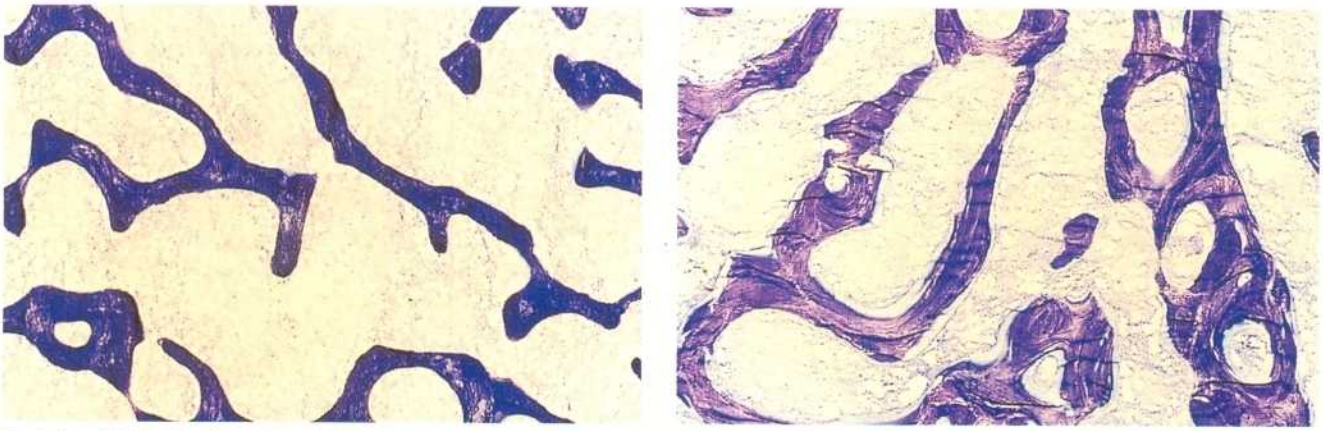

Fig. 2 **Bone biopsy showing normal (left) and osteomalacic (right) bone.**

Paget's Disease

Paget's disease is common and characterized by increased osteoclastic activity which leads to increased bone resorption. Increased osteoblastic activity repairs resorbed bone, but the new bone is laid down in a disorganized way. The clinical presentation is almost always bone pain which can be particularly severe. Serum alkaline phosphatase is high, and urinary hydroxyproline excretion is elevated. These provide a way of monitoring the progress of the disease. Although a viral cause for Paget's disease has been proposed, the aetiology remains obscure.

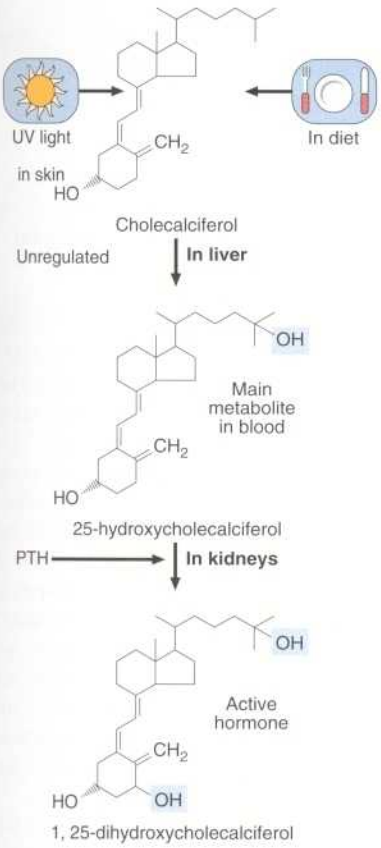

Fig. 3 **The main steps in the metabolism of vitamin D.**

Case history 30

A 66-year-old male presented to the bone clinic with severe pains in his right leg and pelvis. Radiological examination revealed Pagetic lesions in his legs, pelvis and also his skull. Biochemical results in a serum sample were unremarkable except for alkaline phosphatase which was grossly elevated at 2700 U/l. It was decided to treat him with a bisphosphonate drug.

- How would you monitor this patient's response?

Comment on page 155.

OTHER BONE DISEASES

Examples include:

- *Vitamin D dependent rickets, Types 1 and 2.* These are rare bone diseases resulting from genetic disorders leading to the inability to make the active vitamin D metabolite, or from receptor defects which do not allow the hormone to act.
- *Tumoral calcinosis.* This is characterized by ectopic calcification around the joints.
- *Hypophosphatasia.* This is a form of rickets or osteomalacia which results from a deficiency of alkaline phosphatase.
- *Hypophosphataemic rickets.* This is believed to be a consequence of a renal tubular defect in phosphate handling.
- *Osteopetrosis.* This condition is characterized by defective bone resorption.
- *Osteogenesis imperfecta.* Brittle bone syndrome, is an inherited disorder which occurs around once in every 20 000 births.

Diagnosis of these and other rare conditions may require help from specialized laboratories.

BIOCHEMISTRY TESTING IN CALCIUM DISORDERS OR BONE DISEASE

The role of the routine biochemistry laboratory in diagnosis and treatment of patients with calcium disorders and bone disease is to provide measurements of calcium, albumin, phosphate and alkaline phosphatase in a serum specimen as first line tests. Follow-up tests which may be requested include:

- PTH
- magnesium
- urine calcium excretion
- 25-hydroxycholecalciferol
- urine hydroxyproline excretion
- osteocalcin.

Characteristic biochemistry profiles in some common bone diseases are shown in Table 1.

Table 1 **Biochemical profiles in bone diseases**

Disease	Profile
Bone metastases	Calcium may be high, low or normal Phosphate may be high, low or normal PTH is usually low Alkaline phosphatase may be elevated or normal
Osteomalacia/Rickets	Calcium will tend to be low, or may be clearly decreased PTH will be elevated 25-hydroxycholecalciferol will be decreased if the disease is due to vitamin D deficiency
Paget's disease	Calcium is normal Alkaline phosphatase is grossly elevated
Osteoporosis	Biochemistry is unremarkable
Renal osteodystrophy	Calcium is decreased PTH is very high
Osteitis fibrosa cystica (primary hyperparathyroidism)	Calcium is elevated Phosphate is low or normal PTH is increased, or clearly detectable and thus 'inappropriate' to the hypercalcaemia

Bone disease

- Alkaline phosphatase is a marker for bone formation. Urinary hydroxyproline is a marker for bone resorption. Better markers for bone turnover are being evaluated.
- Osteomalacia due to vitamin D deficiency can be confirmed by finding a low 25-hydroxycholecalciferol concentration. In severe disease, alkaline phosphatase will be increased. Calcium may well fall and there will be an appropriate rise in PTH.
- The characteristic biochemical marker of Paget's disease is a grossly increased alkaline phosphatase activity, as a consequence of increased bone turnover.

OSTEOPOROSIS

OSTEOPOROSIS

Osteoporosis is a large public health problem. One in four women and one in twenty men over the age of 60 in Britain will have an osteoporosis related fracture. It is a major cause of morbidity and mortality in the elderly. Almost one third of orthopaedic beds are occupied by patients with this disease which was once dismissed as a normal part of ageing.

Osteoporosis is characterized by a reduction in bone mass per unit volume. The composition of the matrix is essentially normal, but there is just less of it. The cortical areas of bones are thinner than normal and the trabeculae are smaller and less extensive (Fig.1). Both sexes show a gradual bone loss throughout life but women lose bone rapidly in the post-menopausal years. This is called primary osteoporosis and is of unknown aetiology.

Accelerated bone loss leading to secondary osteoporosis may be caused by:

- certain drugs, especially long-term use of corticosteroids or heparin
- immobilization
- smoking
- alcohol
- Cushing's syndrome
- gonadal failure
- hyperthyroidism
- gastrointestinal disease.

Diagnosis

Serial measurements of bone density are required to demonstrate bone loss but frequently on presentation the diagnosis can be made from a single measurement. It may take months or years to quantitate the rate of bone loss with confidence.

For many patients the first indication of the disease is when they suffer a vertebral compression fracture, a fracture of the distal radius or a fractured neck of femur. Crush fractures of vertebrae may occur slowly and relatively painlessly over a period of time (Figs. 2 and 3).

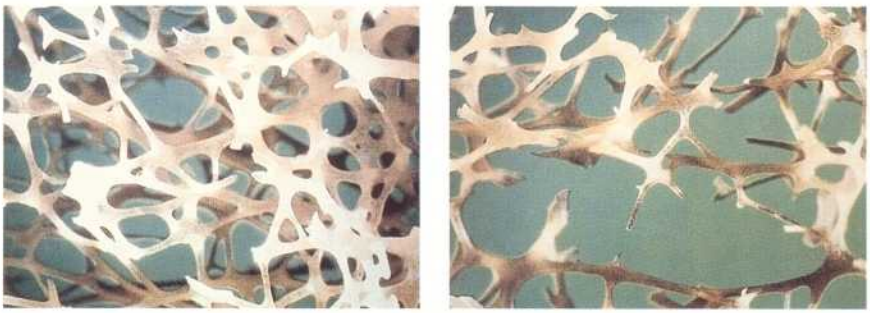

Fig. 1 **Bone showing (a) normal trabeculae and (b) bone loss in osteoporosis.** Reproduced by kind permission of Dr W. Kumthornthip.

The role of the clinical biochemistry laboratory

Biochemical tests cannot be used to diagnose primary osteoporosis or monitor accelerated bone loss because the results of the common biochemical analyses overlap in healthy subjects and patients with the disorder. Biochemical tests are of value in the diagnosis of hyperthyroidism, gonadal failure or Cushing's syndrome which cause secondary osteoporosis.

Osteoporosis may be present alongside osteomalacia (pages 70–71) in which case biochemical monitoring is helpful.

Treatment

Prevention, rather than cure, is the current goal. This should start in childhood with a good diet and exercise. The most powerful predictor of osteoporosis is the skeletal mass at 16 years of age.

Once skeletal maturity has been attained, it is the magnitude of the subsequent bone loss which may lead to osteoporosis. The use of corticosteroid drugs should be minimized. Stopping smoking is important. At the menopause, hormone replacement therapy is of benefit, not only for the relief of menopausal symptoms but also to prevent rapid bone loss. Indeed, cardiovascular protection also follows as an incidental benefit of such therapy.

When osteoporosis is established the treatment options are as yet unsatisfactory. Oral calcium supplements, oestrogens and fluoride have all been advocated. Bisphosphonates may be beneficial.

Fig. 2 **Crush fractures of vertebral bodies from patient with osteoporosis.** Reproduced by kind permission of Dr W. Kumthornthip.

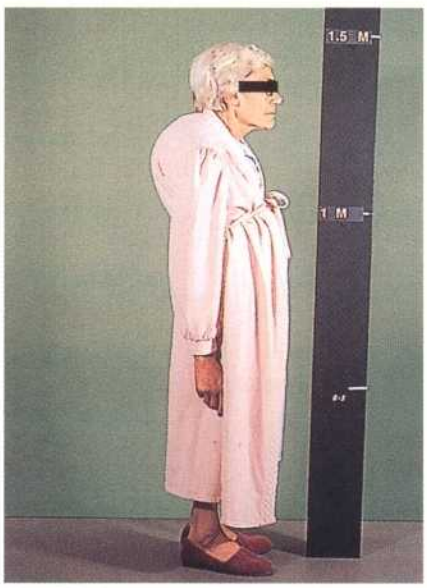

Fig. 3 **Elderly woman with so called 'Dowager's hump' from collapsed vertebrae due to osteoporosis.**

Osteoporosis

- Osteoporosis is a major cause of morbidity and mortality in the elderly.
- It is characterized by a reduction in bone mass per unit volume.
- Although both sexes show a gradual bone loss throughout life, women lose bone rapidly in the post-menopausal years. This 'primary osteoporosis' is of unknown aetiology.
- Bone loss causing secondary osteoporosis may be accelerated by a number of factors such as the use of corticosteroids, smoking and immobilization.