Diagnosis and current management of Paget's disease of bone

Paget's disease of bone is the most common metabolic bone disorder after osteoporosis. The potent new bisphosphonates offer opportunities to suppress disease activity and may have a role in reducing associated morbidity – even in asymptomatic patients.

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Paget's disease of bone is a focal skeletal disorder characterised by increased cellular activity involving osteoclasts and osteoblasts. It is often asymptomatic, remaining unrecognised for decades[1] and progressing to produce significant morbidity in a substantial proportion of sufferers.[2] The changes in bone microarchitecture caused by Paget's disease can lead to pathological fractures or bony deformity. Either a single skeletal site or many sites may be involved – the rates of involvement for different skeletal sites found in a study conducted in 1999 are shown in Figure 1.

The radiological prevalence of Paget's disease increases with age from 2% in men and 1% in women between 55 and 59 years to 20% in men and 7% in women over 85 years. The overall prevalence in the population is about 5%, with recent reports suggesting a decrease in both prevalence and severity.[4,5] There appears to be a slight male predominance, with the ratio of affected women:men between 1:1.4 and 1:1.9.[6]

Marked geographical and regional differences in prevalence have been observed – the disease is more common in Europe, North America and Australia,[5,7-9] which suggests that environmental or genetic factors may be involved in its pathogenesis. Familial clustering is well documented, with an autosomal dominant pattern of inheritance.[10] Between 12 and 40% of patients with Paget's disease of bone have at least one first degree relative who is affected.[11,12] Some studies have demonstrated linkages with loci on chromosome 18[13-17] or 6.[18-19] An analysis of a large Australian kindred, however, has excluded these linkages, a finding which is consistent with Paget's

IN SUMMARY

- **Paget's disease affects about 5% of the overall population with a slight male predominance. Between 12 and 40% of patients with Paget's disease of bone have at least one affected first degree relative.**
- **Measurement of total serum alkaline phosphatase is a simple and sensitive screening test that can also be used to monitor therapy. Screening should be considered in family members with unexplained musculoskeletal symptoms.**
- **In asymptomatic individuals, Paget's disease may be diagnosed either as a result of an elevated alkaline phosphatase finding or as an incidental finding on radiographs.**
- **Bisphosphonate therapy is now regarded as the treatment of choice for symptomatic patients. Potent oral agents taken for three to six months produce long term suppression of disease activity.**
- **Symptomatic disease and preparation for orthopaedic surgery are major indications for bisphosphonate therapy, with potent oral agents offering the potential to modify the course of the disease.**
- **Asymptomatic individuals who have involvement at sites that may be prone to complications should be referred for an opinion regarding use of antiresorptive therapy.**

disease of bone being a genetically heterogeneous disorder.[20]

The observation of virus-like inclusion bodies in pagetic osteoclasts has led to the suggestion that viruses are involved in the aetiology,[21] a hypothesis supported by immunohistochemical and *in situ* hybridisation data.[22,23]

Clinical features of Paget's disease

Musculoskeletal features

The cardinal symptom of Paget's disease of bone is pain described as 'boring' or 'nagging' in character. Generally the pain is not exacerbated by weightbearing but it keeps the patient awake at night. There appears to be little relationship between radiological bone changes and symptoms,[24] with one study showing an association with symptoms for only 30% of 863 pagetic sites in 170 patients.[25] Pain associated with secondary osteoarthritis in joints adjacent to affected bones occurs in about 50% of cases.[25]

Bone affected by Paget's disease may enlarge; weightbearing bones may become bowed and produce deformity (Figure 2). The progression of pagetic lesions is a slow process, with osteolytic lesions in long bones increasing in length by less than 2.5 cm per year. It has been estimated that the typical sabre deformity of the tibia or involvement of the entire skull may take more than 25 years to develop.[1]

The disorganisation of bony architecture in pagetic bone may lead to characteristic fissure fractures (cortical infractions) in the cortices of long bones or, less commonly, complete fractures (Figures 3a and b). The management of such fractures is often complicated.[26]

Neurological features

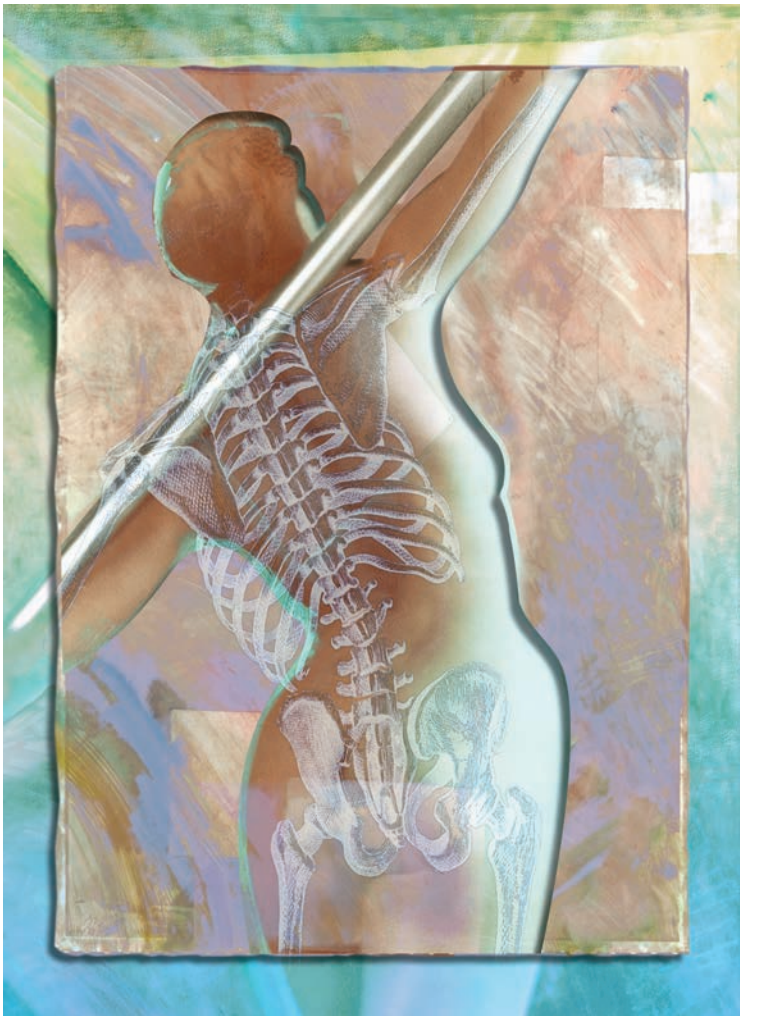
Neurological compression syndromes are serious and not uncommon complications of pagetic involvement of the skull or vertebral column. Invagination of the base of the skull may result in hydrocephalus, long tract signs and lower cranial nerve palsies. The vascularity of pagetic bone may produce vascular steal syndromes.

Deafness is present in 30 to 50% of patients who have skull involvement; vestibular disturbances and tinnitus are much less common. Deafness is believed to be both sensorineural (through involvement of the petrous temporal bone and internal auditory canal) and conductive (through involvement of the ossicles). Direct compression of the auditory nerve is thought to be uncommon. Although the spine is a common site for pagetic involvement, spinal cord dysfunction is rare.[18]

Cardiovascular effects

Pagetic bone is highly vascular – polyostotic disease, in particular, may produce arteriovenous

Paget's disease of bone



Paget's disease of bone is a localised disorder that displays an affinity for the axial skeleton, long bones and skull. A significant proportion of pagetic sites are asymptomatic, but therapeutic choices may be influenced by identifying involvement at sites that might be susceptible to complications.

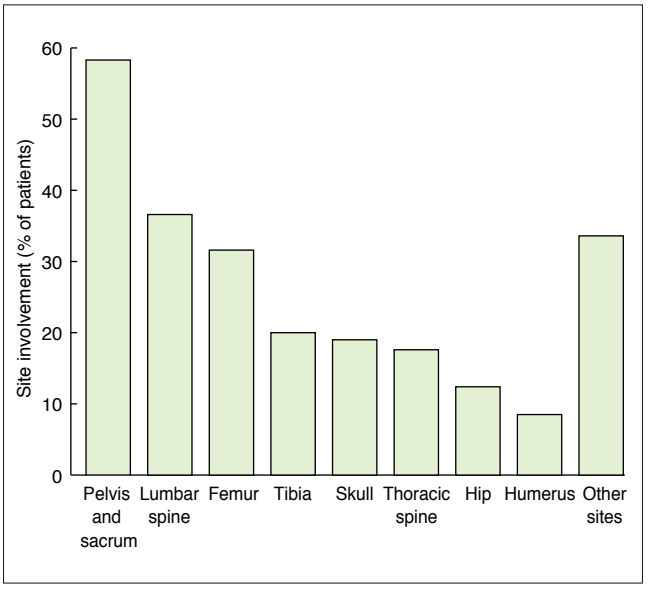


Figure 1. The prevalence of involvement of different skeletal sites in patients with Paget's disease of bone (n=889).[3]

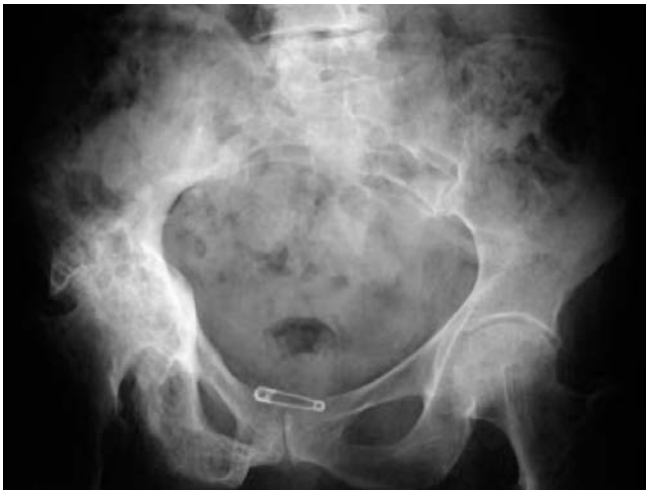


Figure 2. X-ray demonstrating pagetic involvement of the right hemipelvis with severe secondary osteoarthritis and deformity of the acetabular surface of the hip joint, protrusio acetabuli. This patient was a 79-year-old woman who presented with pain and limited movement of the right hip.

shunting that culminates in high output cardiac failure. The increased blood flow through pagetic bone is clinically apparent by an increase in skin temperature and dilatation of superficial veins over affected bones and is sometimes associated with an audible bruit.

Tumours

Rarely, Paget's disease of bone may be complicated by sarcomas. Osteosarcoma is the most common, but fibrosarcomas, chondrosarcomas, reticulosarcomas and pleomorphic tumours have also been described. Sarcomas present with unremitting pain – often unresponsive to analgesics – at the site of the tumour, and prognosis is generally very poor (six-month survival is about 50%).

Benign giant cell tumours may also complicate the disease. These tumours may be sensitive to glucocorticoid therapy.

Metabolic effects

Hypercalcaemia may complicate extensive Paget's disease, particularly if there has been immobilisation, and the frequency of nephrolithiasis may be increased. The serum uric acid level may be elevated, but it remains unclear whether gout is more common in patients with Paget's disease.[18]

Radiological features

Characteristically, pagetic bone has a mixed appearance showing areas of osteolysis and sclerosis. Lytic changes appear to predominate in early lesions, with flame-shaped resorption fronts in long bones or osteoporosis circumscripta in the skull. Bone volume may be increased, particularly in the spine and the shafts of long bones. Progression of disease within a radiologically involved site may occur, but the involvement of new bony sites is uncommon after radiological diagnosis.

Radionuclide bone scanning is a sensitive method for identifying affected bones and should be performed at the time of diagnosis (Figure 4). However, the changes seen on a radionuclide scan are nonspecific: positive scans can also occur with degenerative changes adjacent to joints or with malignancy. Plain x-ray examination of areas of increased radionuclide is therefore required to confirm the sites of involvement. Identification of asymptomatic sites that might be susceptible to complications may influence therapeutic choices.

Repeated scans are generally unnecessary, except for monitoring monostotic disease if biochemical markers are normal. The frequency of radiological follow up will depend on the site (or sites) of involvement, the presence of active areas of osteolysis, cortical infractions or fissure fractures, and the risk of new fracture. New symptoms or significant worsening of symptoms also warrant further radiological evaluation to differentiate between the development of cortical infractions, fracture and bone tumours.

Biochemical markers

Laboratory evaluation centres around biochemical markers of bone turnover. Total serum alkaline phosphatase is elevated in 95% of patients with Paget's disease and correlates with the extent of skeletal involvement.[27] In most clinical situations, it is a sensitive and specific marker of disease activity.

In patients with monostotic disease

or coexisting abnormalities in liver function, measurement of bone formation markers may be useful.[28] Serum bone gla-protein (osteocalcin), a specific osteoblast protein, lacks sensitivity in Paget's disease.[29]

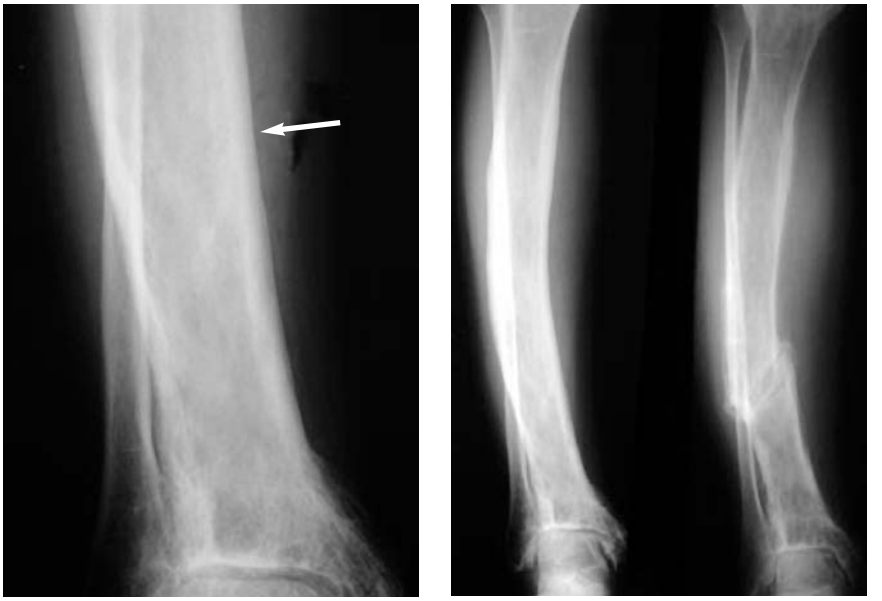
Urine hydroxyproline excretion reflects bone resorption and correlates with the extent of disease; however, it is influenced by dietary protein (requiring patients to be fasting or taking a protein-modified diet when specimens are collected) and is not as strongly associated with the extent of the disease as total alkaline phosphatase.[25] Degradation products of collagen, serum or urine crosslinks are useful markers of bone resorption that are not influenced by dietary protein and are valuable in the assessment of limited disease.[28] Recent observations that urine C-telopeptide (CTX) undergoes β-isomerisation in lamellar bone and, to a lesser extent, in woven pagetic bone suggests that the α-CTX:β-CTX ratio may be a specific means of monitoring treatment. Bisphosphonate therapy decreases this ratio, which is consistent with the replacement of woven bone with lamellar bone.[30]

Monitoring of disease activity and the response to therapy can be undertaken using biochemical markers with measurements taken at intervals of four to six months. If the prevention of complications is to be the therapeutic goal, prolonged suppression of disease activity with at least a normalisation of biochemical markers is likely to be necessary. The nadir in the serum alkaline phosphatase level may occur several months after completing a course of therapy.[31]

Diagnosis

Paget's disease should be suspected in patients who have unexplained musculoskeletal symptoms, particularly those who have a family history of the disorder. In asymptomatic individuals, the diagnosis may be made as a result of investigation for an elevated alkaline phosphatase level or as an incidental finding on radiographs. A combination of deformity, bony enlargement, coarsening of trabeculae and a mixture of osteolytic and osteosclerotic areas in a patient with elevated biochemical markers of bone turnover is highly suggestive of Paget's disease. Given the availability of a simple, inexpensive and effective screening test (total serum alkaline phosphatase level) and effective therapy, screening of family members should be considered.

Problems in diagnosis arise in patients who have limited skeletal involvement or normal biochemical markers – these patients should be referred for specialist assessment. Monostotic vertebral Paget's disease must be distinguished from vertebral haemangioma, fibrous dysplasia,



Figures 3a and b. X-rays showing evolution of an insufficiency fracture in a patient who presented with increasing pain in the lower left leg. a (left). At presentation, a cortical infraction (arrow) was visible on the medial surface of the tibia. b (right). Extension of the fracture in the left tibia three months later.

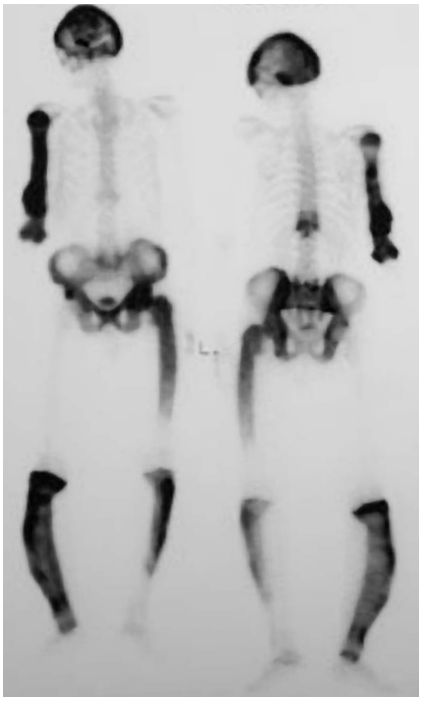


Figure 4. A whole body bone scan demonstrating increased radionuclide uptake (left, anterior; right, posterior). The changes are typical of Paget's disease of bone – the skull, right humerus, T12, pelvis, both tibiae and left femur are affected. Note the area of expansion of the distal right humerus caused by a periosteal reaction (differential diagnosis would include osteosarcoma) and the sabre deformity of the right tibia.

Using bisphosphonate therapy to treat Paget's disease of bone

The bisphosphonates are stable pyrophosphate analogues that inhibit osteoclastic bone resorption by several mechanisms,[41] producing prolonged suppression of bone turnover.[42] They are targeted to pagetic bone and concentrated at sites of increased bone remodelling.[42] A comparison of the bisphosphonates available to treat Paget's disease of bone in Australia is given in the Table below.

First generation therapy

Etidronate (Didronel) was the first bisphosphonate used to treat Paget's disease. However, it was soon shown to produce mineralisation defects and, in high dosage, to be associated with fracture.[43] Etidronate is contraindicated in patients with renal failure, a history of osteomalacia, and cortical infractions or severe lytic lesions that might predispose to fracture.

Second generation therapy

Pamidronate (Aredia) is a second generation bisphosphonate. It has approximately 100 times the antiresorptive activity of etidronate and, in most patients, can achieve prolonged normalisation of biochemical markers of bone turnover for at least one year.

Pamidronate is usually administered intravenously because of gastrointestinal side effects.[44] Many treatment regimens have been reported, but the optimal one remains unclear. The infusion may result in a transient increase in bone pain at affected sites; after the first dose, patients may develop pyrexia or influenza-like symptoms lasting up to about 72 hours. Rarely, an anterior uveitis may occur that settles spontaneously when therapy is ceased. Mineralisation defects have been reported, but these were not associated with any clinical sequelae and may simply reflect the marked changes in bone turnover associated with potent inhibition of bone resorption.[45-46]

Third generation therapies

Orally active agents that are more potent are now entering clinical practice, with alendronate (Fosamax), tiludronate (Skelid) and risedronate (Actonel) now available on the PBS. A six-month course of alendronate (40 mg daily) normalises bone turnover markers in more than 60% of patients, with evidence of radiological improvement in 48% of cases and normal deposition of new lamellar bone in biopsy samples.[47]

Oral alendronate appears to be more effective than etidronate or salcatonin and to have an efficacy similar to intravenous pamidronate – oesophagitis has been reported, but the risk can be reduced by taking the drug with a full glass of water while being in an upright position and remaining upright until eating. Alendronate should be avoided in patients who have impaired swallowing or abnormal oesophageal motility,[48] and discontinued in any patient if oesophageal symptoms occur.

Shorter courses of therapy have been explored using tiludronate and risedronate.[49,50] Tiludronate taken for three months (400 mg daily) normalises biochemical markers in 35% of patients without impairing mineralisation and has a lower incidence of upper gastrointestinal side effects.[49] Treatment with risedronate using one or two cycles of three months' duration normalises alkaline phosphatase in more than 50% of subjects.[50]

Table. The bisphosphonates: a comparison of features

	Suggested dosage	Administration	Efficacy*	Potential adverse effects
Etidronate	400 mg daily for 6 months	Oral	17%	Impaired bone mineralisation Osteomalacia Pathological fracture with high dose
Pamidronate	Single 60 mg infusion, repeated when clinically indicated	Intravenous	38%†	Transient flu-like symptoms Asymptomatic hypocalcaemia Temporary exacerbation of bone pain Reactions at site of infusions
Alendronate	40 mg daily for six months	Oral	63 to 80%	Upper gastrointestinal intolerance Oesophagitis, with or without ulceration Temporary exacerbation of bone pain
Tiludronate	400 mg daily for three months	Oral	35%	Mild gastrointestinal disturbance
Risedronate	30 mg daily for two months	Oral	>50%	Mild gastrointestinal disturbance

* Percentage of patients reaching normal levels of serum alkaline phosphatase after initial course of treatment. † Based on daily infusions of 60 mg for three days.

malignancy and infiltrative processes (e.g. sarcoidosis), osteomyelitis and compression fractures. In an older patient who has bone pain, elevated biochemical markers of bone turnover and a positive bone scan but doubtful radiological changes, metabolic bone diseases such as osteomalacia and hyperparathyroidism should be considered.

Drug treatment

The mainstay of medical management is inhibition of bone resorption using calcitonin (e.g. salcatonin [Miacalcic], which is salmon calcitonin) or a bisphosphonate, which reduce the accelerated bone turnover characteristic of Paget's disease. Limited data indicate that these treatments can improve symptoms, bone histology and radiology.

In symptomatic patients, pain relief is the primary objective of therapy. Mild reductions in biochemical markers achieved using calcitonin or the earlier bisphosphonates do not prevent the development of new complications, but are of benefit in reducing symptoms in the short term. In a study of 34 patients who were free of complications at the time of enrolment, 62% developed complications during 12 years of follow up.[2] Thus, active Paget's disease affecting sites where complications may develop (weightbearing bones, extensively involved skull, vertebral bodies and areas adjacent to major joints), is currently regarded by many as an indication for therapy. There are, however, few data evaluating the long term effect of antiresorptive therapy on the risk of complications, and specialist referral is suggested to assess the need for therapy in asymptomatic patients.

Calcitonin therapy may slow the progression of hearing loss[32] and reverse neurological complications.[33] Data from one study (which was performed without controls) suggest that bisphosphonate therapy may reduce the incidence of fracture in pagetic bone,[34] and improvement in bony deformity in a patient with skull and facial deformity has been reported.[35] The optimum strategy may be to treat as early as possible with a view to halting disease progression by normalising bone turnover. Continuous treatment with alendronate over a two-year period has been reported to normalise the bone scan appearance in about one-third of patients.[36]

Restoration of normal bone architecture is likely to represent the optimal strategy for reducing complications. Among patients who achieve and maintain normal levels of bone turnover markers, the possibility of reducing or halting disease progression seems likely. Thus, in an era when effective agents to suppress bone resorption have become available, a secondary goal of treatment may be to prevent disease progression and the development of complications. Whether prolonged suppression of disease activity with antiresorptive agents will reduce the occurrence of complications remains to be established, and enthusiasm for potent disease suppressing therapies in asymptomatic patients should be tempered by the fact that the majority of sufferers are elderly and often have multiple comorbidities.

Calcitonin

Calcitonin inhibits osteoclastic bone resorption directly, relieving bone pain and suppressing disease activity.[37] Healing of lytic lesions, conversion of woven bone to lamellar bone, and reversal of neurological complications have been reported with calcitonin therapy.[33] A 50% reduction in pretreatment biochemical markers of bone turnover occurs over four to six months; normalisation will occur in some patients.

To treat Paget's disease, calcitonin needs to be given by subcutaneous injection because intranasal administration has low bioavailability and generally does not provide adequate suppression of bone resorption.[38] Although it is rapidly effective, calcitonin is limited by troublesome side effects: nausea and flushing occur in 20 to 30% of patients; vomiting, diarrhoea, abdominal pain and local reactions at injection sites are not infrequent. Reducing the dosage may reduce side effects, and tolerance to these reactions usually develops. However, the parenteral route of administration, frequency of side effects and development of bisphosphonates have largely relegated calcitonin therapy to being a treatment of historical interest.

The bisphosphonates

The potent third generation bisphosphonates suppress bone turnover for one to two years before biochemical markers begin to increase slowly above normal values,[39,40] and bisphosphonate therapy is now regarded as the treatment of choice for symptomatic patients. The agents available in Australia to treat Paget's disease of bone are listed in the box on page 22.

Other agents

Other therapies directed at symptomatic relief have a role in Paget's disease, including analgesics and NSAIDs. Given the propensity for gastrointestinal side effects associated with the use of potent

bisphosphonates, use of COX-2 inhibitors for associated osteoarthritis is likely to have advantages over other NSAIDs.

Surgical treatment

Orthopaedic surgery is indicated for preventing impending fracture. It is also indicated for existing fracture and, given that conservative therapy is associated with a high risk of delayed union or nonunion, open reduction may be necessary. Osteotomy may be indicated to correct bowing deformities, whereas joint replacement may be necessary to treat osteoarthritis complicating Paget's disease of bone. Neurosurgical intervention may be required for managing spinal cord compression, spinal stenosis and complications of basilar invagination.

The use of antiresorptive agents prior to elective orthopaedic surgery is recommended to reduce vascularity and the risk of hypercalcaemia.

Monitoring and follow up

Monitoring of bone turnover, usually by measurement of alkaline phosphatase at intervals of four to six months, has been suggested. If normalisation is achieved, re-treatment starting when levels increase to 20 to 25% above the upper limit of normal is suggested; if alkaline phosphatase fails to normalise, re-treatment starting when values increase to 25% above the nadir is suggested.[51] Secondary resistance to bisphosphonate therapy represents a potential limitation to long term disease suppression.[52,53]

Summary

Paget's disease is a chronic condition that requires prolonged follow up and monitoring and may involve medical and orthopaedic specialists. Bisphosphonate therapy is now the treatment of choice for symptomatic disease, with potent new orally active agents suppressing bone turnover for up to one or two years.

The long latency and propensity for complications have led to questioning of traditional management, in which therapy has been reserved for symptomatic patients. Whether long term suppression of disease activity can reduce the risk of complications is yet to be established, but several lines of evidence suggest that it can be achieved. Screening of family members and patients with unexplained musculoskeletal symptoms with measurement of serum alkaline phosphatase should be considered. The management of patients with complications may require a multidisciplinary approach. MT

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A guide to the diagnosis and current management of Paget's disease of bone

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