The current status of Paget's disease of the bone

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Paget's disease is a metabolic bone disease characterized by abnormalities of bone turnover, structure and architecture. The disease is of unknown aetiology, although both genetic and environmental factors have been implicated. Treatment is indicated for patients with active disease and currently bisphosphonates are the first-choice management option.

Paget's disease is the second most common metabolic bone disease in UK. Since it was first described in 1877 by Sir James Paget, understanding of the disease and its pathophysiology has increased considerably. The advent of bisphosphonate treatment has also provided effective therapeutic agents for the management of patients with Paget's disease. This article reviews the recent progress that has been made in this disease area, assesses current practice, and also highlights future areas for research and development.

Paget's disease is currently the second most common metabolic bone disease in the UK, outstripped only by osteoporosis. The disease rarely becomes clinically evident before the age of 40 years, and shows an exponential increase in prevalence with age. The disease prevalence in the UK is estimated at 5% in those aged 55 years and over, rising to upwards of 10% in those aged 95 years (van Staa et al, 2002). Epidemiological data suggest that over the last 20 years there has been a decline in both the incidence of the disease and its severity (Cooper et al, 1999). The cause of this decline is not apparent, but suggests that a possible environmental agent may be an important activator in the disease process. Most studies (Kanis, 1998) have reported a slight sex bias, with men affected slightly more frequently than women, with ratios ranging from 7:6 to 2:1.

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PATHOPHYSIOLOGY

Paget's disease is a focal disorder of bone metabolism, primarily caused by an increase in osteoclast-related bone resorption. Increased bone resorption is coupled with a vigorous osteoblastic response which causes abundant new bone formation in association with increased vascularity. The newly formed bone may be woven or lamellar in type (usually with abnormal spatial orientation), lacking the structural organization of the normal trabeculae and hence having greater flexibility and less resistance to deformation. Paget's disease is also usually associated with local enlargement of bone, suggesting that abnormal modelling is also involved in the disease process. The combination of structural and architectural bone abnormalities, in conjunction with biomechanical forces, accounts for the majority of the disease's clinical manifestations and complications.

The initial stimulus for increased bone turnover is unknown. Studies have suggested a possible viral aetiology for Paget's disease, as pagetic osteoclasts have been found to contain paramyxoviral-like nuclear inclusions. The measles virus and the canine distemper virus have both been implicated as the paramyxovirus present in pagetic osteoclasts and their precursors, although to date viral material has not been isolated and the pathophysiological role of these viruses is controversial.

Paget's disease has a familial tendency, suggesting a possible genetic cause for the disease (Leach et al, 2001). In patients with Paget's disease, 30–40% have a first-degree relative similarly affected. In addition, several pedigrees have been identified where Paget's disease appears to be segregating as an autosomal dominant trait. Linkage analysis within these kindreds has identified several potential candidate loci on chromosomes 2, 5, 6, 9, 10 and 18, with evidence of heterogeneity between families. It is also probable that there are gene–environmental interactions resulting in disease onset and localization.

Receptor activator of nuclear factor kB (RANK) and its ligand (RANKL) are newly described members of the tumour necrosis factor superfamily, and have been identified as being critical to osteoclastogenesis. The RANK gene maps to

chromosome 18, and to date an insertional mutation within the first exon of the RANK gene has been found to segregate with Paget's disease in one kindred (Hughes et al, 2000). However, screening of sporadic cases with Paget's disease has failed to identify any mutations within the RANK gene or find any association between the disease and gene polymorphisms. Further work is needed in this area to clarify the role of the RANK gene in the aetiology of Paget's disease.

CLINICAL FEATURES

Paget's disease can have a wide spectrum of clinical presentations, ranging from asymptomatic to painful, disabling and, very rarely, life-threatening (Kanis, 1998). In most cases (>80%), however, the disease is asymptomatic and is only diagnosed on the basis of an isolated increase in serum alkaline phosphatase or on classical radiological appearances following imaging. The clinical presentation also depends on the skeletal sites affected by pagetic lesions and their activity. Any part of the skeleton may be affected, but most commonly involved are the pelvis, femur, lumbar spine, skull and tibia. The complications arising from Paget's disease can be attributable to local and systemic factors (*Table 1*).

The most frequent symptom in patients with Paget's disease is bone pain. It has been suggested that this is the result of both increased vascular supply and of periosteal stretching caused by local bone growth. Pagetic pain is classically described as insidious and boring in nature, not usually aggravated by movement, and only progresses slowly. Sometimes, the pain also coexists with bone deformity and enlargement. In some cases it is difficult to differentiate between pain caused by Paget's disease and that caused by secondary osteoarthritis and degenerative disease. Primary bone pain must also be differentiated from pain associated with certain clinically significant complications, i.e. fractures and sarcomatous change.

Painful fissure fracture (or pseudofracture) and complete pathological fracture occur in areas of high mechanical stress, particularly in the weight-bearing bones of the lower limbs. Fractures in pagetic bone usually follow very minimal trauma. The great majority of these are located in the subtrochanteric region or shaft of the femur and, less often, in the upper third of the tibia. Occasionally they are also seen at other sites such as the forearm, humerus or pelvic brim. Prolonged immobilization should be avoided following fractures in patients with Paget's disease as it can accelerate bone loss (leading to osteoporosis and an increased fracture risk) and can provoke hypercalciuria and hypercalcaemia.

Sarcoma arising in pagetic bone is the most serious complication of the disease, although it is a rare event, affecting less than 1% of Paget's patients. Sarcomatous change should be suspected when severe pain of sudden onset arises in bone known to have been previously affected by the disease. Such pain is usually unresponsive both to analgesics and medical therapy aimed at suppressing pagetic disease activity. Other indications of a possible sarcoma include swelling at the tumour site, which may enlarge rapidly, and a significant rise in the serum total alkaline phosphatase. At present the prognosis for patients with Paget's disease who develop sarcoma is poor with neither chemotherapy nor radical surgery having any significant effect on long-term survival.

MEDICAL MANAGEMENT

Historically medical treatment for Paget's disease has been reserved for the symptomatic management of pain in patients with active disease or as an adjunct to surgery in those with serious complications (i.e. spinal cord compression). There are now a number of therapies which have been successfully used to suppress abnormal osteoclast activity and control bone turnover. The most widely available are calcitonin and the bisphosphonates, with the newer bisphosphonates able to effectively and safely suppress disease activity (Miller et al, 1999). With the advent of these

TABLE 1.
Complications associated with Paget's disease

Focal	Skeletal	Bone pain
		Bone enlargement
		Bone deformity
		Dental involvement
	Articular	Secondary osteoarthritis
	Neurological	Deafness
		Hydrocephalus
		Nerve root compression
		Spinal cord compression
		Pagetic steal syndrome
Local	Fractures	Fissure
		Pathological
	Malignancy	Sarcoma
		Giant cell tumour
Systemic	Cardiovascular	High output cardiac failure
	Metabolic	Hypercalcaemia and/or hypercalciuria following immobilization
		Secondary hyperparathyroidism
	Skeletal	Increased vertebral fracture risk

TABLE 2.
Pharmaceutical agents currently licensed for the treatment of Paget's disease in the UK

Agent	Route	Dose and duration	Treatment interval (months)
Calcitonin	Subcutaneous or intramuscular injection	50 units 3 times weekly, to 100 units daily	–
Etidronate	Oral	5 mg/kg daily for 6 months	Can be repeated after 3 months
Tiludronate	Oral	400 mg daily for 12 weeks	Can be repeated after 6 months
Pamidronate	Intravenous	30 mg weekly for 6 weeks (total dose 180 mg), or 30 mg first dose then 60 mg alternate weeks (total dose 210 mg), or total 360 mg (in divided doses of 60 mg) per treatment course	Can be repeated at 6-monthly intervals
Risedronate	Oral	30 mg/day for 2 months	May be repeated if necessary after at least 2 months

agents, there is now a move to treat the disease earlier in patients whose disease is only mildly active or those who are asymptomatic (Selby et al, 2002). It remains unclear, however, whether aggressive treatment of Paget's disease to normalize disease activity (as assessed by serum alkaline phosphatase or radionucleotide imaging) will result in fewer long-term complications. This hypothesis is currently being evaluated in a large prospective 3-year study in the UK.

Treatments currently licensed for the management of Paget's disease in the UK are detailed in *Table 2*. Clinical trials are currently ongoing with agents such as zoledronate (a potent intravenous bisphosphonate) and the results of these studies are awaited with interest.

KEY POINTS

- Paget's disease is the second most common metabolic bone disease in the UK, affecting up to 5% of those aged 55 years and over.
- Genetic factors appear to play an important role in disease aetiology, with some families showing the disease segregating as an autosomal dominant trait.
- Mutations within the RANK gene have been found in some cases of familial Paget's disease, although variation within this gene does not appear to be important in cases of sporadic Paget's disease in the general population.
- Bisphosphonates are effective in the management of patients with active Paget's disease with or without symptoms.
- Prolonged suppression of disease activity may reduce longer term complications, e.g. fracture, deafness and secondary osteoarthritis.
- Total joint arthroplasty at the hip and knee is effective in Paget's disease patients with symptomatic secondary osteoarthritis that has failed to respond to conventional medical treatments.
- All patients with Paget's disease should have access to specialist medical and surgical care to ensure that they benefit both from the new and effective treatments that are now available for their condition.

SURGICAL MANAGEMENT

Surgery may be necessary for patients with severe complications. The most common indication for surgery is patients with secondary osteoarthritis whose pain is not adequately controlled with medical therapies. Total joint arthroplasty at both the hip and knee has been shown to be effective and safe in these patients. There has been concern that the operative procedures may be more difficult with surgery involving pagetic bone, and although not evidence based many patients receive bisphosphonate treatment preoperatively in an attempt to suppress disease activity and reduce local complications. This requires further evaluation.

Although there has been long-term (between 5 and 10-year) follow-up of Paget's patients undergoing total hip arthroplasty, only limited data are available for those with total knee arthroplasty and again research is needed in this area. Most reported studies regarding surgical outcome have focused on specialist centres, and it remains to be determined if outcomes are equivalent at other less specialized orthopaedic units.

CONCLUSIONS

Paget's disease is the second most common bone disease, affecting up to 5% of those aged over 55 years. It is commonly asymptomatic, although it can be associated with significant morbidity. Bisphosphonates are the treatment of choice for patients with active Paget's disease, and research is assessing whether aggressive management of disease may reduce long-term complications. There is growing information regarding the aetiology of Paget's disease, with genetic factors appearing to play an important role. Improved understanding of pathophysiology in Paget's disease will hopefully lead to improved and earlier diagnosis, preventative strategies to reduce disease incidence, and the development of novel therapeutic options for those with the disease. HM

Conflict of interest: Dr Keen is an investigator for a Novartis sponsored trial examining the use of zoledronic acid in the management of active Paget's disease.

Cooper C, Schafheutle K, Dennison E et al (1999) The epidemiology of Paget's disease in Britain: is the prevalence decreasing. *J Bone Miner Res* **14:** 192–7

Hughes AE, Ralston SH, Marken J et al (2000) Mutations in TNFRSF11A affecting the signal peptide of RANK cause familial expansile osteolysis. *Nature Genet* **24:** 45–9

Kanis JA (1998) *Pathology and Treatment of Paget's Disease of Bone.* Martin Dunitz, London

Leach RJ, Singer FR, Rodman GD (2001) The genetics of Paget's disease of the bone. *J Clin Endocrinol Metab* **86:** 24–8

Miller D, Brown JP, Siris ES et al (1999) A randomised, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. *Am J Med* **106:** 513–20

Selby P, Davie M, Ralston S, Stone M (2002) Guidelines on the management of Paget's disease of bone. *Bone* **31:** 366

van Staa TP, Selby P, Leufkens HG, Lyles K, Sprafka JM, Cooper C (2002) Incidence and natural history of Paget's disease of bone in England and Wales. *J Bone Miner Res* **17:** 465–71