ABSTRACT

Paget’s disease of bone is a common disorder characterized by increased but disorganized bone remodelling accompanied initially by an increase in osteoclastic bone resorption followed by a secondary increase in osteoblastic activity. Paget Disease of Bone (PDB) was first described by Sir James Paget in 1877 in a paper describing the clinical features of a disorder he called ‘osteitis deformans’. Some patients are asymptomatic but others present with bone pain or other complications such as broken bones, deformity, hearing loss and pinched nerves in your spine. Diagnosis is usually based on biochemical markers of bone turnover, radionuclide bone scan and radiological examination.

Bisphosphonates, in particular zoledronic acid, are regarded as the treatment of choice for paget’s disease of bone. Major advances have been made in understanding the pathophysiology of paget’s disease in recent years and highly effective agents are now available which suppresses the abnormal bone turnover that causes the disease. Here we review recent advances in the epidemiology, pathogenesis, clinical features, prevention and management of paget’s disease and we also reflect upon the future challenges that remain to be overcome to explain the unusual distribution of the disease and to favourably alter the natural history and its complications.

KEYWORDS: Paget’s disease, Bone resorption, Bisphosphonate, osteoclast.

INTRODUCTION

Paget’s disease of bone (PDB) is a chronic disorder, characterised by focal areas of excessive osteoclastic bone resorption accompanied by a secondary increase in osteoblastic bone formation resulting in a mosaic pattern of lamellar bone. Normal bone is replaced by a disorganized, hypertrophic and softened osseous structure that is prone to deformity and fracture. The classical description was by Sir James Paget in 1877 who described the clinical
presentation and course of the disease in five patients naming the condition ‘Osteitis Deformans’. Tremendous advances have been made in the understanding of the causes of PDB over recent years and treatments have been developed that are highly effective at suppressing the elevated bone turnover that is characteristic of the disease. Here we review recent advances in the epidemiology, pathogenesis, clinical features, investigation and management of PDB as well as what the future holds with regards to new directions for research and for developing targeted treatments.[1]

ETIOLOGY
The UK has the highest rates of paget’s disease in the world. It’s also relatively common in countries with high levels of migration from Britain such as Australia, New Zealand and South Africa. Paget’s disease is an age related condition and rarely affects young people. It is estimated about 5% of white adults aged over 55 have the condition in the UK with a slight male preponderance.[2] Recent studies from the United Kingdom and New Zealand suggest that the incidence of Paget’s disease is falling, perhaps by as much as 50% over the past 20 years and that the severity of newly diagnosed cases is falling.[3,4] Although the etiology of PDB is unknown, the disease may be caused by genetic factors and/or slow virus infection. A family history is present in about 15% of the patients and first-degree relatives of the patients have a sevenfold increase in risk of developing the disease.[5,6]

SYMPTOMS
Most people who have Paget's disease of bone experience no symptoms. When symptoms do occur, bone pain is the commonest complaint of the disease.[7,8] It is classically described as unrelenting, more severe at night, not worsened by exercise and not alleviated with rest. The disease may affect only one or two areas of your body or may be widespread. Patients with PDB require thorough clinical assessment to determine the likely cause of the pain. Other presentations include deformity, fractures and neurologic complications such as headache, hearing loss, nerve compression syndromes and spinal stenosis. PDB is associated with a substantially increased risk of osteosarcoma but this complication is rare occurring in less than 0.5% of patients.[7,8] Secondary osteoarthritis is also common. This is thought to be due to a combination of abnormal biomechanical loading of joints due to deformity and osteosclerosis affecting subchondral bone. Your signs and symptoms will depend on the part of your body that's affected, including.

- **Pelvis**: Paget's disease of bone in the pelvis can cause hip pain.
Skull: An overgrowth of bone in the skull can cause hearing loss or headaches.

Spine: If your spine is affected, nerve roots can become compressed. This can cause pain, tingling and numbness in an arm or leg.

Leg: As the bones weaken, they may bend causing you to become bowlegged. Enlarged and misshapen bones in your legs can put extra stress on nearby joints, which may cause wear-and-tear arthritis in your knee or hip.

Major clinical features include:

Skeletal
* bone pain
* Deformity
* Fracture
* Secondary osteoarthritis
* Dental complications
* Primary bone tumours

Skeletal/neurological
* Deafness.\(^{[9-14]}\)

Neurological
* Cranial nerve palsies
* Spinal stenosis
* Hydrocephalus

Others
* Vascular steal syndromes
* High output cardiac failure
* Immobilisation hypercalcaemia
* Cardiac valvular calcification.\(^{[15,16]}\)
Fig. 1 Symptoms of paget’s disease of the bone; Paget’s disease, showing involvement of the skull and limbs.

ETIOLOGY
Studies of patients with Paget’s disease indicate that there is a family history of the disorder in 5% to 40% with most researchers reporting a 10–20% incidence.[17,18]
Genetic factors
Most of the implicated genes are known to play a role in osteoclast differentiation and function. The most important susceptibility gene for classical PDB is SQSTM1.\cite{19} It has been estimated that 40% of patients with a family history of PDB and 10% of patients with ‘sporadic’ PDB carry a mutation in this gene.\cite{20,21} The causal mutations cluster in the ubiquitin associated (UBA) domain of the protein and inhibit its ability to bind ubiquitin. This in turn causes upregulation of NFkB signalling and osteoclast activation.\cite{20} Other candidate genes for classical PDB include CSF1, which encodes macrophage colony-stimulating factor (M-CSF), TNSRSF11A, which encodes RANK, OPTN, which encodes optineurin and TM7SF4, which encodes DC-STAMP.\cite{22} Activating mutations in TNFRSF11A cause the syndromes of familial expansile osteolysis and early onset familial Paget’s disease;\cite{20} loss of function mutations in TNFRSF11B causes juvenile PDB;\cite{20} and loss of function mutations in VCP cause the syndrome of inclusion body myopathy, Paget’s disease and fronto-temporal dementia.\cite{23} Patients with SQSTM1 gene mutations have more severe and extensive disease and a higher rate of complications than patients without SQSTM1 mutations.\cite{19,22}

Environmental factors
The most widely studied potential environmental trigger for PDB is viral infection. The viral hypothesis stemmed from the observation that PDB osteoclasts frequently contain inclusion bodies that were thought to resemble the paramyxovirus nucleocapsid.\cite{20,23} Other predisposing environmental triggers include dietary calcium deficiency during childhood,\cite{24} vitamin D deficiency and childhood rickets;\cite{25} excessive mechanical loading of the skeleton\cite{26} and environmental pollutants.\cite{27}

DIAGNOSIS
The diagnosis of PDB is often suspected by the finding of a raised serum Alkaline Phosphatase (ALP) or on the basis of the typical x-ray findings of osteosclerosis and osteolysis.\cite{28,29}

1. Diagnostic imaging
Paget’s disease is diagnosed primarily by radiological examination. Early in the course of the disease, lytic activity predominates, causing focal osteolytic lesions (osteoporosis circumscripta) or flameshaped, advancing lytic wedges in the long bones. Subsequently, areas of sclerosis develop, leading to the characteristic appearances of mixed lytic and sclerotic
areas, thickened trabeculae, bone expansion, cortical thickening and deformity. An isotope bone scan is recommended in all patients as part of the initial diagnostic assessment to determine the distribution of the disease, in particular the involvement of sites with the potential for complications, such as base of skull, spine and long bones. Computed tomography scanning is helpful to assess skull-base involvement (including patients with deafness), spinal stenosis or other neurological complication.

Isotope bone scanning in Paget’s disease

![Isotope bone scan](image)

Fig. 2 A patient with polyostotic Paget’s disease, showing involvement of the skull, left scapula, thoracic vertebrae (T7, T9 and T11), left femur and right calcaneum.

2. Biochemistry

Plasma total alkaline phosphatase level is the most clinically useful marker of disease activity. In patients with monostotic or limited disease, the level may be in the upper reference range, thus a normal alkaline phosphatase level does not exclude the disorder. Liver function tests should be performed, in particular measurement of $\gamma$-glutamyltranspeptidase level, as liver disease can also result in elevated alkaline phosphatase activity, causing diagnostic confusion. In patients whose total alkaline phosphatase level is not elevated and in those with liver disease, measurement of bone-specific alkaline phosphatase level or urine markers of bone resorption is helpful.

TREATMENT

Paget’s disease is treatable, but not all patients require treatment. Drugs that suppress bone turnover (antiresorptive treatments) can be helpful in treating pain that is due to increased
metabolic activity, but most patients also require analgesics and some require surgery to treat complications of the disease such as fractures and osteoarthritis.

**Antiresorptive treatments**

Treatment with Bisphosphonates: Bisphosphonates are the treatment of first choice for metabolically active PDB.\textsuperscript{[23,30,31]} Bisphosphonates acts by binding to hydroxyapatite in bone matrix, thereby inhibiting the dissolution of crystals. They prevent osteoclast attachment to the bone matrix and osteoclast recruitment and viability.

**Zoledronate**

- Zoledronic acid has been shown to be superior to risedronate at suppressing biochemical markers of bone turnover in PDB.\textsuperscript{[32]}
- 5 mg of Zoledronate intravenously over 15-30 minutes can be used. One dose may be effective for many years therefore often patients may not require further treatment.

**Calcitonin**

- Calcitonin is recommended for treatment of Paget disease if bisphosphonates are contraindicated. This agent is a peptide hormone that binds to calcitonin receptors on osteoclasts and rapidly inhibits bone resorption. Osteoclasts do not induce cytotoxic effects in bone cells.
- The recommended course will depend on how well you respond to treatment, although it usually lasts between 6 and 18 months.

**Pamidronate**

- Pamidronate is given 60 – 90 mg by slow intravenous infusion over 2-4 hours. A single dose of 60mg is adequate for some patients with mild disease\textsuperscript{[33,34]} whereas two to four doses (and occasionally more), administered days or weeks apart, are required for more severe disease.

**Oral preparations**

**Risedronate**

Risedronate is prescribed one 30 mg tablet daily for 2 months which is taken on an empty stomach with a full glass of water, first thing in the morning. Advise the patient not to lie down after taking the tablet.
Side-effects of all the three drugs include:

- Flu like symptoms can occur 24-48 hours after infusion and treatment can be associated with bone and joint pains.
- Rarely - inflammation of the eyes.
- Zolendronate may cause hypercalcemia in patients with high bone turnover and pre-existing vitamin D deficiency. Thus as a precaution vitamin D levels are measured and calcium and vitamin D supplements may be given prior to treatment.
- Infusion with Zolendronate can occasionally be associated with atrial fibrillation.
- Osteonecrosis of the jaw has been rarely reported.
- Bisphosphonates are contra-indicated in patients with significant renal impairment. In these circumstances subcutaneous calcitonin (100 u s/c three times weekly) can be tried.\[35,36\]

Non-pharmacological treatments

- Patients with bone deformity and limb shortening can benefit from shoe raises.
- Splints or braces to support your bones and joints and to help keep weak bones from breaking can be used.
- A cane or walker to help you avoid falling and breaking a bone
- Surgical treatment may also be necessary to treat complications. Results are generally good, but the procedures can be technically challenging due to bone deformity, osteosclerosis and increased vascularity.\[25\]
- Prevent falls - Paget's disease puts you at high risk of bone fractures. Remove slippery floor coverings, use nonskid mats in your bathtub or shower.
- Eat well - diet includes adequate levels of calcium and vitamin D, which facilitates the absorption of calcium. This is especially important if you're being treated with bisphosphonates.
- Exercise regularly - Exercising on a regular basis is essential for maintaining joint mobility and bone strength.

**FUTURE DIRECTIONS**

The ZiPP study (Zoledronate in the Prevention of Paget’s) trial aims to determine if genetic testing can be combined with bisphosphonate therapy to prevent or delay the onset of Paget’s disease in people with abnormalities of the SQSTM1 gene. The ZIPP study is important since it will provide a proof of concept that complications can be prevented. If successful the same
approach could be used for other people with a family history of Paget’s who do not have SQSTM1 abnormalities”.

CONCLUSION
Paget disease is a bone disease which may be symptomatic initially and it can be diagnosed by its classic radiographic features and an early diagnosis can prevent potential complications such as pathological fracture, arthritis, hearing loss and other neurological complications, osteosarcoma. Advances in treatment have resulted in the availability of bisphosphonates which produces normal or near bone turn-over indices in a majority of patients. Some patients continue to be resistant to bisphosphonates and further work on newer anti-resorptive agents continues. Further work is required to fully understand the molecular mechanisms by which the genetic variants that have been identified cause PDB. Research is also needed to determine if early intervention can alter the natural history of the disease and prevent complications. Finally, it is important to identify the environmental triggers that predispose to PDB and understand how they interact with genetic factors to influence susceptibility and disease severity.

REFERENCE


