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Paget's disease of bone

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Summary

Paget's disease of bone is a common disorder characterized by increased but disorganized bone remodelling. Some patients are asymptomatic but others present with bone pain or other complications such as fracture and deformity. Major advances have been made in understanding the pathophysiology of Paget's disease in recent years and highly effective agents are now available with which to suppress the abnormal bone turnover that causes the disease. Here we review recent advances in the epidemiology, pathogenesis, clinical features and management of Paget's disease. 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 prevent the development of complications.

Introduction

Paget's disease of bone (PDB) is a common metabolic disease characterized by increased and disorganized bone turnover affecting one or more skeletal sites. 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'.[1] 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 developments 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.

Epidemiology

There are marked ethnic and geographical variations in the occurrence of PDB. The highest prevalence is found in the United Kingdom (UK), but the disease is also common in Spain, Italy, France, North America, Australia and New Zealand.[2–4] Within these countries there are also localized areas of higher prevalence such as the North West of England[4] and Vitugudino in Spain.[5] In the UK, PDB affects between 1% and 2% of the population aged 55 and over but the prevalence increases with age to affect ~8% of the population by the eighth decade.[2–4] The high frequency of PDB in Australia and New Zealand is thought to be attributable to the migration of white British nationals to these countries in the early 18th–20th centuries. Conversely, PDB is rare in the Indian subcontinent, Southeast and East Asia as well as in Scandinavia.[2–5]

A recent systematic review of the epidemiology of PDB concluded that the incidence and severity of new cases of PDB has declined in recent years in most countries with the exception of Italy.[5] The cause of this is unclear but changes in global migration patterns with an increased immigration from areas of low incidence such as South Asia to the UK and North America; a more sedentary lifestyle, improved nutrition and reduced exposure to infections have all been offered as possible explanations for this phenomenon.[5]

Pathogenesis

Bone turnover is markedly increased in bones that are affected by PDB, Osteoclast numbers, size and nuclearity are all increased and bone formation is also elevated. Accumulating evidence suggests that the elevated bone turnover in PDB is caused by abnormalities in the molecular pathways that regulate osteoclast activity as discussed below.

Osteoclast differentiation and function is critically dependent on interactions between three molecules; Receptor Activator of Nuclear Factor Kappa B (RANK) which is encoded by the *TNFRSF11A* gene, RANK ligand (RANKL), encoded by the *TNFSF11* gene and Osteoprotegerin (OPG), encoded by the *TNFRSF11B* gene. The RANK receptor is expressed by osteoclasts and osteoclast precursors; RANKL is produced by osteocytes, activated T-cells, osteoblasts and bone marrow stromal cells and OPG is produced by osteoblasts and other cell types.[6,7] Binding of RANKL to RANK promotes osteoclast differentiation and bone resorption whereas OPG inhibits these processes by acting as a decoy receptor for RANKL.[6,7] In PDB, osteoclast precursors have increased sensitivity to RANKL resulting in enhanced osteoclast activation and bone resorption. The increased rates of bone formation in PDB are thought to be secondary to the increase in bone resorption but there is some evidence that cells of the osteoblast lineage may also be abnormal.[8] Although bone formation is increased in PDB, the newly formed bone is abnormal and has reduced mechanical strength, predisposing to the occurrence of fractures and deformity.[7]

Genetic factors

Linkage studies in families and genome-wide association studies have identified several genes and loci that predispose to PDB and related syndromes. Most of the implicated genes are known to play a role in osteoclast differentiation and function (Figure 1).

The most important susceptibility gene for classical PDB is *SQSTM1*.[9] A wide variety of mutations have now been identified and 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.[7,23] The causal mutations cluster in the ubiquitin associated (UBA) domain of the protein and inhibit it's ability to bind ubiquitin. This in turn cause upregulation of NFκB signalling and osteoclast activation by mechanisms that are still incompletely understood.[7] 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.[10]

The genetic basis of several rare syndromes with clinical features that mimic PDB have also been clarified. Activating mutations in *TNFRSF11A* cause the syndromes of familial expansile osteolysis and early onset familial Paget's disease;[7] loss of function mutations in TNFRSF11B causes juvenile PDB;[7] and loss of function mutations in VCP cause the syndrome of inclusion body myopathy, Paget's disease and fronto-temporal dementia.[6]

These observations indicate that genetic variations in the pathways that regulate osteoclast activity are most likely responsible for the abnormalities of osteoclast morphology and activity that are characteristic of PDB and related syndromes.

From a clinical perspective, patients with SQSTM1 gene mutations have more severe and extensive disease and a higher rate of complications than patients without SQSTM1 mutations.[9,11] It has also been noted that risk alleles have additive effects, resulting in a higher risk of developing PDB and more extensive disease in those that carry the highest number of risk alleles.[10,11]

Environmental factors

Environmental factors are also important in PDB as reflected by the fact that incidence and severity of the disease have reduced in many countries over recent years.[7] 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. However attempts to isolate viral nucleic acids from affected tissue have yielded contradictory results.[6,7] Other suggested predisposing environmental triggers include dietary calcium deficiency during childhood;[12] vitamin D deficiency and childhood rickets;[13] excessive mechanical loading of the skeleton[14] and environmental pollutants.[15]

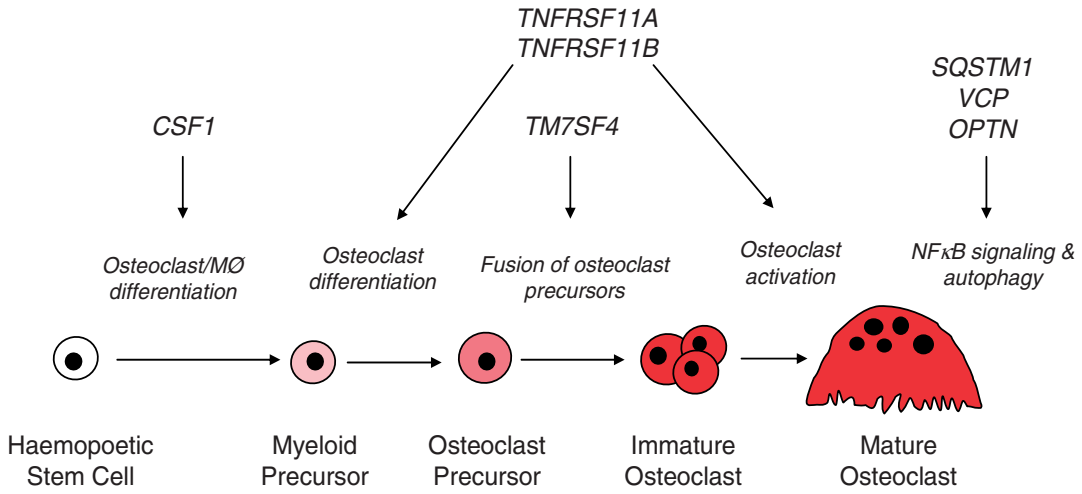

Figure 1. Genes that predispose to Paget's disease and related syndromes. Candidate genes for PDB and related syndromes are shown. The *CSF1* gene, which encodes M-CSF, promotes differentiation of stem cells to cells of the osteoclast/macrophage lineage. The *TNFRSF11A* and *TNFRSF11B* genes encode RANK and OPG, respectively; both proteins play a key role in regulating osteoclast differentiation and activity. The *TM7SF4* gene is essential for fusion of osteoclast precursors to form mature osteoclasts. The *SQSTM1*, *VCP* and *OPTN* gene products all play roles in regulating NFκB signalling and autophagy in osteoclasts and are thought to play a role in osteoclast activation. (adapted from Ralston and Layfield[7]).

Clinical features

Bone pain is the commonest symptom of PDB.[16,17] It is classically described as unrelenting, more severe at night, not worsened by exercise and not alleviated with rest. However these features are not always present in clinical practice and it is often difficult to differentiate the pain of PDB from that of complications such as co-existing osteoarthritis. Therefore patients with PDB require thorough clinical assessment to determine the likely cause of the pain. This is important as treatments such as bisphosphonates only help pain that is due to increased metabolic activity.

Other presentations include deformity, fractures and neurologic complications such as headache, hearing loss, nerve compression syndromes and spinal stenosis[16,17] PDB is associated with a substantially increased risk of osteosarcoma but this complication is rare occurring in less that 0.5% of patients.[16,17] 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.

Sometimes PDB may be picked up as an incidental finding in patients who are having blood tests or x-rays for another reason. A previous population-based survey in the UK suggested that ~7% of patients with radiological evidence of PDB come to medical attention.[3] We have recently found that about 15% of patients come to medical attention in our region and of those that do, about 78% have symptoms or signs (Tan A.J.H. and Ralston S.H., unpublished)

Investigations

The diagnosis of PDB is often suspected by the finding of a raised serum Alkaline Phosphatase (ALP) in patients who have otherwise normal liver function, or on the basis of the typical x-ray findings of osteosclerosis and osteolysis disrupting the normal trabecular pattern in affected bone, cortical thickening and bone expansion.[2,18] The most frequently affected bones are the pelvis (70% of cases), femur (55%), lumbar spine (53%), skull (42%) and tibia (32%).[6,18] Bone scintigraphy is a useful technique to evaluate the extent of disease and can be followed up by targeted x-rays of abnormal areas that are symptomatic.

Serum total ALP is most commonly used to assess metabolic activity. Bone-specific ALP can also be used but offers no clear advantage over total ALP except in patients with liver disease.[19]

Management

The management of PDB requires a multidisciplinary approach. 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

Bisphosphonates are the treatment of first choice for metabolically active PDB.[6,20,21] Randomized trials comparing the effects of different bisphosphonates in the treatment of PDB have generally been short in duration and focused on the effects of treatment on biochemical markers of bone turnover. These studies have shown that the newer, more potent nitrogen-containing bisphosphonates are more effective than older bisphosphonates at suppressing bone turnover but few differences have emerged in symptomatic response between treatments.

Zoledronic acid has been shown to be superior to risedronate at suppressing biochemical markers of bone turnover in PDB and to improve some quality of life measures although the magnitude of effect was small.[22]

In another study intensive therapy with the bisphosphonate risedronate had no greater effect on quality of life, bone pain, deafness, fracture rates or the requirement for orthopaedic surgery as compared with symptomatic therapy despite the fact that ALP levels were much lower in the risedronate group.[23] This indicates that levels of bone turnover do not correlate well with symptom response or complications in PDB.

Nowadays, most clinicians favour the use of aminobisphosphonates over older bisphosphonates such as etidronate and tiludronate because of their greater efficacy at suppressing bone turnover. The most popular treatments are oral risedronate (30 mg daily for 2 months); intravenous pamidronate (60 mg on one to three occasions) and intravenous zoledronic acid (5 mg).

Intravenous bisphosphonates are associated with a transient flu-like illness and also carry a risk of inducing hypocalcaemia in patients with high bone turnover and pre-existing vitamin D deficiency. Because of this patients should be checked for vitamin D deficiency and given supplements if necessary.

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.[2] There are anecdotal reports of successful treatment of PDB with the RANKL inhibitor Denosumab[24] but the drug is unlicensed for this indication.

Repeated courses of antiresorptive drugs can be given as necessary if symptoms recur in association with an elevation in ALP levels.

Other medical treatments

Additional medications may be required to control pain. A variety of treatments are used in clinical practice including simple analgesics, opiates, gabapentin and amitriptyline.

Non-pharmacological treatments

Patients with bone deformity and limb shortening can benefit from shoe raises and walking aids. 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]

Clinical guidelines

Current clinical guidelines recommend that the main indication for bisphosphonate therapy is treatment of bone pain thought to be due to increased metabolic activity of PDB.[2] There is no evidence as yet that bisphosphonates can prevent complications or alter the natural history of PDB.

Future directions

Further work is required to fully understand the molecular mechanisms by which the genetic variants that have been identified cause PDB and to clarify why the disease occurs in a focal manner. 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.

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