Paget's disease of bone: a review of epidemiology, pathophysiology and management

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***Abstract*:** Paget's disease of bone is a common disorder which may affect one or many bones. Although many patients are asymptomatic, a variety of symptoms and complications may occur. Fortunately, effective pharmacologic therapy, primarily with potent bisphosphonates, is now available to treat patients with complications or symptoms. This review of Paget's disease of bone will include epidemiology and pathophysiology, complications and clinical findings, indications for treatment, and the drugs currently available to treat this condition.

***Keywords*:** Paget's disease of bone, bisphosphonates, osteoclasts

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Introduction

Paget's disease of bone (PDB), which is also known as osteitis deformans, was first described by Sir James Paget more than 130 years ago [Paget, 1877]. Paget's disease is a common focal skeletal disorder that may involve a single bone (monostotic) or multiple bones (polyostotic). Although many PDB patients are asymptomatic, significant symptoms including bone pain, bone deformity, secondary arthritis, and neurologic problems occur in some patients. Treatment with calcitonin [Avramides, 1977; Singer, 1977] was developed in the 1970s and more recently very effective therapy with newer bisphosphonates [Silverman, 2008] has become available.

Epidemiology

PDB is the second most common bone remodeling disease after osteoporosis. This condition occurs in 1–2% of white adults older than 55 years [Ralston *et al.* 2008]. An analysis of archeological skeletons from Northern England (900–1850) [Rogers *et al.* 2002] found an overall prevalence of PDB of 2.1% in cases older than 40 years. The prevalence before 1500 was 1.7% and after 1500 was 3.1%. The prevalence of PDB increases with age and is slightly more common in men. PDB is rare under 25 years and unusual before 40 years of age [Siris and Roodman, 2008]. In a survey of 864 patients the mean age at diagnosis was 58 years [Siris, 1991]. The prevalence differs amongst various ethnic/geographic groups. This disease is most common in the United Kingdom and Western Europe but is also common in British immigrants to Australia, New Zealand, South Africa, and South America [Altman, 2002]. The disease is uncommon in African blacks, Scandinavia, China, Japan, Southeast Asia, and the Indian subcontinent [Altman, 2002]. Furthermore, there is evidence of decreasing incidence and severity of PDB in the United Kingdom [Cooper *et al.* 1999, 2006] and New Zealand [Doyle *et al.* 2002; Cundy *et al.* 2004; Cundy, 2006] over the past 25–30 years. The incidence of PDB does not appear to have clearly decreased in United States [Tiegs *et al.* 2000] or Spain [Guanabens *et al.* 2008]. In Italy, the incidence has remained fairly stable [Gennari *et al.* 2005], however, the severity of disease may have increased in Southern Italy during recent years [Rendina *et al.* 2006]. First-degree relatives of patients with PDB have an increased risk of PDB, particularly if the patient has an early age of diagnosis or deforming bone disease [Siris *et al.* 1991]. Family history is positive in approximately 15–30% of patients with PDB and first degree relatives of patients with PDB have about a sevenfold greater risk for the development of Paget's disease [Siris and Roodman, 2008]. Familial PDB also tends to be diagnosed at a younger age and involve more of the skeleton than sporadic disease [Seton *et al.* 2003].

These findings suggest that genetic and environmental factors are important in the development of this disease.

Pathophysiology

PDB is a chronic, progressive disorder involving one or more bones. Skeletal lesions of PDB are characterized by increased osteoclastic bone resorption, increased but somewhat disorganized bone formation, and increased vascularity of bone [Ralston *et al.* 2008]. The osteoclasts are increased in number and size and may contain more nuclei than normal. The nuclei may contain inclusion bodies that resemble viral particles [Roodman, 1996].

The initial lesion is believed to be a focal increase in osteoclastic bone resorption. This is followed by accelerated bone formation. Because of the accelerated bone turnover, new collagen fibers are not laid down in an orderly linear fashion but rather in a disorganized manner. The resultant bone is a mosaic of woven and lamellar bone [Siris and Roodman, 2008] that is mechanically insufficient and at increased risk for fracture or deformity.

PDB is considered to be a disease of the osteoclasts [Wirfel *et al.* 1999]. Bone marrow and circulating osteoclast precursors demonstrate increased sensitivity to factors known to stimulate bone resorption such as 1,25 dihydroxy vitamin D and receptor activator of NF-kB ligand (RANKL) [Roodman and Windle, 2005]. Increased interleukin-6 (IL-6) expression and signaling may contribute to increased osteoclastic activity [Roodman *et al.* 1992; Hoyland *et al.* 1994]. RANKL (which stimulates osteoclastic differentiation) expression is increased in pagetic marrow cells [Menaa *et al.* 2000] and elevated levels of circulating RANKL were found recently in PDB patients [Martini *et al.* 2007]. Osteoblasts are increased in numbers at pagetic sites, however, they are morphologically normal and are not considered to be a primary pathophysiologic factor in PDB by most authorities [Singer *et al.* 2006].

Environmental factors

Several potential environmental factors have been associated with the development of PDB. Rural life and animal contacts are associated with a greater risk of PDB in Italy [Gennari *et al.* 2006] and Spain [Lopez-Abente *et al.* 1997] suggesting that animals may carry infectious agents. Viral infection has been suggested because the nuclear inclusion bodies in osteoclasts appear to represent viral nucleocapsids [Mills and Singer, 1976]. Paramyxovirus, and in particular canine distemper virus and measles virus are the most extensively studied environmental agents, however controversy remains whether viruses play a role in the development of PDB. Some studies suggest an association between PDB and dog ownership [O'Driscoll and Anderson, 1985] and in particular dogs not vaccinated for canine distemper [Khan *et al.* 1996]. Other studies refute this association [Siris *et al.* 1990; Seton *et al.* 2003]. Another study found an association between prior dog and possibly prior cat ownership and PDB in patients younger than 60 years [Holdaway *et al.* 1990]. *In situ* hybridization (ISH) [Basle *et al.* 1986] and reverse transcriptase polymerase chain reaction (RT-PCR) [Reddy *et al.* 1995, 1996; Friedrichs *et al.* 2002] have suggested the presence of measles virus nucleocapsid sequences in pagetic osteoclasts and mononuclear cells. Canine distemper virus RNA has also been found using ISH [Gordon *et al.* 1991] and RT-PCR in pagetic bone cells [Gordon *et al.* 1992; Mee *et al.* 1998]. Furthermore, transfection of measles virus nucleocapsid gene into osteoclast precursors produces a pagetic-like phenotype [Kurihara *et al.* 2000, 2006]. Infection of osteoclast precursors with canine distemper virus induces osteoclastogenesis [Selby *et al.* 2006]. Addition of canine distemper virus to canine bone marrow cultures results in an increase in multinucleated osteoclast-like cell formation [Mee *et al.* 1995]. Other studies using RT-PCR, ISH, and immunocytochemistry do not find evidence of measles or canine distemper virus in bone biopsies, bone marrow, or peripheral blood mononuclear cells from PDB patients [Ralston *et al.* 1991; Birch *et al.* 1994; Helfrich *et al.* 2000; Ralston *et al.* 2007]. In a study of bone marrow cultures from patients with PDB, measles virus and canine distemper virus transcripts were not found [Ooi *et al.* 2000]. The reasons that some studies find viral transcripts and others do not are unclear, however, this difference does not appear to be due to assay sensitivity [Ralston *et al.* 2007]. The possibility of contamination as a cause for false positive results has been raised [Ralston *et al.* 2007]. Of note is that serologic evidence of canine distemper virus is absent in patients with PDB and PDB is rare in some regions where canine distemper

virus is common [Cundy and Bolland, 2008]. The issue of whether or not viral infections are related to PDB is not resolved.

Other environmental exposures have been postulated to increase the risk of PDB. Arsenic used as pesticides in the cotton industry from 1917 to 1945 has been hypothesized to contribute to the high regional incidence of PDB in Lancashire, United Kingdom in 1974 and decline in this region by 1993 [Lever, 2002].

Genetic factors

As mentioned above, patients with PDB often report a history of PDB in first-degree relatives. Before discussing the genetics of PDB and related disorders, is appropriate to review the RANK ligand/RANK/OPG system seen in Figure 1 [Deftos, 2005]. This system regulates osteoclast function [Boyle *et al.* 2003]. RANK (receptor activator of NF-kB) is present on osteoclast precursors. Rank ligand (RANKL), which is expressed in the marrow stroma and on osteoblasts, binds RANK on osteoclast precursors promoting osteoclast proliferation and differentiation. Osteoprotegerin (OPG) is a decoy receptor which binds RANKL, thus preventing RANKL from binding RANK. OPG, therefore, inhibits osteoclast differentiation.

Juvenile PDB (also known as hereditary hyperphosphatasia) is associated with inactivating mutations in OPG (TNFRSF11B) [Whyte *et al.* 2002]. Loss of this decoy receptor for RANK results in increased binding of RANK to RANKL and therefore increased osteoclastic differentiation/activity. OPG mutations not appear to be a common cause of classical Paget's disease, however, common polymorphisms of this gene may be associated with PDB in women [Daroszewska *et al.* 2004; Beyens *et al.* 2007].

Activating mutations of RANK (TNFRSF11A) cause familial expansile osteolysis [Hughes *et al.* 2000], expansile skeletal hyperphosphatasia [Whyte and Hughes, 2002], and early onset Paget's disease [Nakatsuka *et al.* 2003]. Mutations of RANK do not appear to be a common cause of classical PDB [Wuyts *et al.* 2001].

The genetics of classical PDB have been reviewed elsewhere [Lucas *et al.* 2006a; Ralston, 2008]. Genome wide-searches and linkage analysis have resulted in the discovery of several possible Paget's susceptibility genes (PDB1–PDB7). These loci are PDB1 (chromosome 6) [Tilyard *et al.* 1982], PDB2 (chromosome 18q21) [Cody *et al.* 1997; Haslam *et al.* 1998], PDB3 (chromosome 5q35) [Laurin *et al.* 2001; Hocking *et al.* 2001], PDB4 (chromosome 5q31) [Laurin *et al.* 2001], PDB5 (chromosome 2p36) [Hocking *et al.* 2001], PDB6 (chromosome 10p13) [Hocking *et al.* 2001; Lucas *et al.* 2008], and PDB7 (chromosome 18q23) [Good *et al.* 2002]. Some of these loci may be false positives and others may represent genes that interact with other genes to cause or modify PDB [Ralston, 2008]. It has been suggested that the PDB7 locus may represent a gene that lowers the age of onset of PDB [Good *et al.* 2004]. Evaluation of patients with PDB3 (chromosome 5q35) mutations resulted in the discovery that the sequestosome 1 (SQSTM1) mutations are an important cause of PDB [Laurin *et al.* 2002; Hocking *et al.* 2002]. SQSTM1 gene mutations have been found in several populations [Lucas *et al.* 2006]. A meta-analysis found SQSTM1 gene mutations in 28.8% of familial and 6.1% of sporadic PDB patients [Rhodes *et al.* 2008]. SQSTM1 codes for p62 which ultimately plays a role in osteoclast regulation [Hiruma *et al.* 2008; Chamoux *et al.* 2009]. Recent studies have differed on whether somatic mutations of SQSTM1 are found in the affected bone of sporadic PDB patients. In a study of pagetic bone samples, none of 22 patients without germline SQSTM1 mutations had somatic SQSTM1 mutations [Matthews *et al.* 2009]. In another recent study, two of five patients without germline SQSTM1 mutations had somatic SQSTM1 mutations in pagetic bone and three of five pagetic osteosarcoma patients without germline SQSTM1 mutations had somatic SQSTM1 mutations in the tumor [Merchant *et al.* 2009]. Interestingly, patients in families with SQSTM1 mutations appear to have variable expressivity and incomplete penetrance of PDB and this mutation may predispose to rather than cause PDB [Leach *et al.* 2006]. In addition to SQSTM1, the evidence for PDB6 (chromosome 10p13) as a candidate gene, appears to remain the strongest [Lucas *et al.* 2008].

The rare syndrome of PDB inclusion body myopathy and frontotemporal dementia is caused by mutations in valosin-containing protein (VCP) [Watts *et al.* 2004; Kimonis and Watts, 2005; Watts *et al.* 2007; Viassolo *et al.* 2008]. Mutations in this gene do not appear to be the

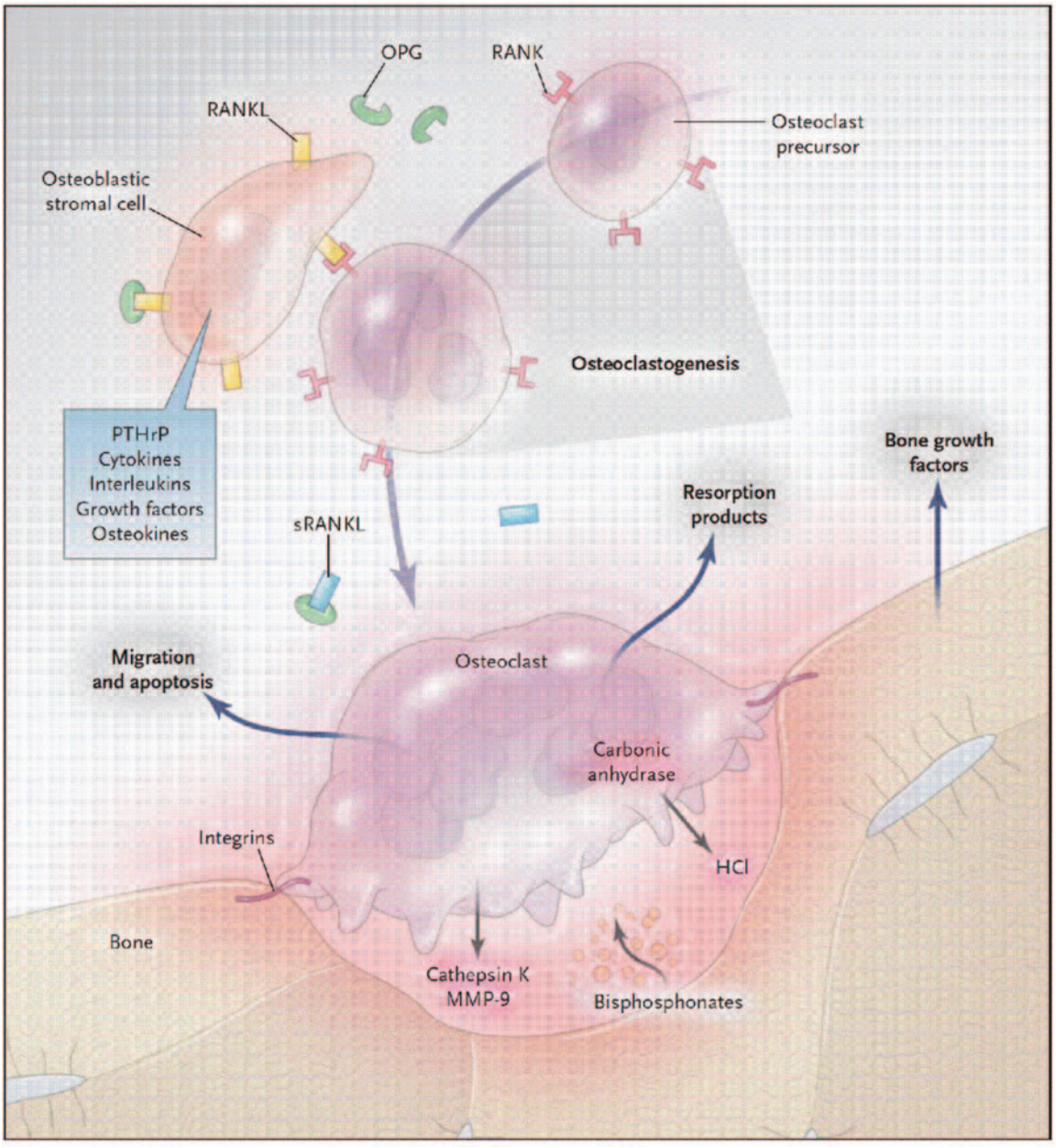

Figure 1. Biology of the osteoclast in bone metabolism as a model for drug discovery.
When bone is resorbed, growth factors in the bone matrix are released, often stimulating osteoclasts, which secrete resorption products into the circulation. Osteoblastic stromal (mesenchymal) cells and maturing osteoclasts express a soluble version of the osteokine-receptor activator of the nuclear factor κB ligand (sRANKL), its cell-bound receptor RANK, and osteoprotegerin (OPG), which sustain osteoclastogenesis. The stimulatory activity of RANKL and the inhibitory effects of OPG regulate osteolysis. Bisphosphonates concentrated under the osteoclasts inhibit resorptive function and promote osteoclast apoptosis. The incorporation of bisphosphonates into bone may increase resistance to resorption. Current therapies for hyperresorptive states can be accommodated by this model; the pathways outlined here suggest additional targets, for which therapies are under development: bone growth factor antagonists; guanine nucleotide exchange factors (GEFs), which inhibit cell migration; arginine–glycine–aspartic acid peptides, which act on integrins; carbonic anhydrase inhibitors, which block the generation of hydrochloric acid; cathepsin K and matrix metalloproteinase 9 (MMP-9) inhibitors; and antibodies to parathyroid hormone-related protein (PTHrP) and RANKL. (With permission from Deftos L.J. (2005). Treatment of Paget's disease — taming the wild osteoclast. *N Engl J Med* 353: 872–875).

cause of common familial or sporadic PDB [Lucas *et al.* 2006a].

Clinical presentation, findings, and complications

Complications of PDB are listed in Table 1. PDB is often asymptomatic and is frequently discovered incidentally when an elevated serum alkaline phosphatase (SAP) is found on routine laboratory testing, or radiographically on x-rays performed for unrelated reasons. A recent population-based study from Olmsted County, Minnesota, USA [Wermers *et al.* 2008] found that 58% of the patients had symptoms at diagnosis. Seventy-two percent of these patients had polyostotic disease. Skeletal complications included bowing deformity in 7.6%, fracture of pagetic bone in 9.7%, and osteosarcoma in 0.4%. Osteoarthritis was present in 73%. Hearing loss was present in the 61%. Neurologic symptoms were uncommon. Overall survival was slightly better than predicted. PDB appears to have an adverse effect on some domains of quality of life [Gold *et al.* 1996; Langston *et al.* 2007].

The most commonly involved bones include the pelvis, femur, spine, skull, and tibia [Siris, 1991]. The upper extremities, clavicles, ribs and scapulae are less frequently affected and the hands and feet are rarely involved [Siris, 1991]. This disease may involve one or more bones, however, it is unusual for a new bone to become involved after initial diagnosis [Cundy and Bolland, 2008]. PDB may be associated with osteoarthritis [Altman and Collins, 1980; Altman, 1999] in large joints such as the hip and knee, particularly when PDB involvement is adjacent to the joint or when bone deformity is present. Bone pain may be present and may be worse at night. Bone pain may be worse with weight-bearing if there is an osteolytic lesion [Whyte, 2006]. Bone enlargement or deformity may be present. There may be enlargement of the skull or frontal bossing and long bones may be bowed [Siris and Roodman, 2008]. When bowed, the femur and tibia typically bow anteriorly and laterally. Bowing of a femur or tibia can lead to pain due to gait abnormalities and arthritis [Siris and Roodman, 2008]. Painful fissure fractures may occur [Redden *et al.* 1981] and are more often on the convex surface of a bone. For example, fissure fractures of the femur are usually found laterally, unlike Looser zones of osteomalacia which are typically seen in the medial aspect of the proximal femur. Pain that increases dramatically may represent a fracture. Patients may note warmth of the skin over pagetic lesions due to increased vascularity. Dilated scalp veins may be present when there is skull involvement.

Table 1. Complications of Paget's disease of bone.

Musculoskeletal
Bone pain
Bone deformity
Fractures
Osteoarthritis of joints adjacent to pagetic bone
Neurologic
Hearing loss
Headache
Cranial nerve deficits
Basilar invagination
Spinal stenosis
Spinal vascular steal syndrome
Peripheral neuropathies
Cardiovascular
Congestive heart failure
Calcification of the aortic valve
Conduction abnormalities
Vascular calcification
Endocardial calcification
Neoplastic
Sarcomas
Giant cell tumors
Miscellaneous
Peyronie's disease
Hypercalciuria
Hypercalcemia

Neurologic complications of PDB have been reviewed elsewhere [Schmidek, 1977; Poncelet, 1999; McCloskey and Kanis, 2002; Rubin and Levin, 2009]. Some symptoms and neurologic complications may be related to skull involvement. Patients with skull involvement may have headaches [Siris and Roodman, 2008]. Cranial nerve deficits have been reported but appear to be rare. Optic atrophy, ophthalmoplegia, anosmia, trigeminal neuralgia, and facial palsy have been reported [Rubin and Levin, 2009]. Hearing loss may occur when the temporal bone is involved. Presbycusis and PDB affect similar populations and it may be difficult to differentiate presbycusis from pagetic hearing loss [Bone, 2006]. Pagetic hearing loss is sensorineural which is greater at high pitches and characteristically accompanied by low-frequency 'air-bone gap' [Monsell, 2004]. The hearing loss appears to be caused by loss of bone density in the cochlear capsule [Monsell *et al.* 1999; Monsell, 2004]. Some patients may have tinnitus. Another neurologic complication

resulting from skull involvement is basilar invagination from softening of the skull base which may cause cause hydrocephalus with headache and dizziness. This basilar invagination can result in syringomyelia and compression of the brainstem. This neurologic syndrome is usually slowly progressive and symptoms may include ataxia, vertigo, tinnitus, dysphagia, and dysarthria [Rubin and Levin, 2009].

Spinal involvement may cause pain, neurologic symptoms, and even paralysis. These may be caused by a compression of the spinal cord or nerve roots as well as ischemia due to 'vascular steal' [Herzberg and Bayliss, 1980]. Peripheral neuropathies such as ulnar, median, sciatic, and posterior tibial have been reported [Rubin and Levin, 2009]. Neurologic symptoms may improve with calcitonin [Chen *et al.* 1979; Herzberg and Bayliss, 1980] or bisphosphonate [Wallace *et al.* 1995; Pane, 2007] therapy.

High output heart failure is rare but may occur with extensive PDB, particularly when underlying cardiac disease is present [Siris, 1991]. Decreased peripheral vascular resistance and increased stroke volume was found in echocardiographic study of PDB [Morales-Piga *et al.* 2000]. Increased frequencies of aortic stenosis [Strickberger *et al.* 1987; Hultgren, 1998] and conduction abnormalities have been reported [Hultgren, 1998]. Increased calcification of the vasculature has also been reported [Laroche and Delmotte, 2005].

Osteosarcomas or other sarcomas (chondrosarcoma, fibrosarcoma) are the most serious complications of PDB. Although these sarcomas are more common than in age-matched controls, they occur in less than 1% of patients with PDB [Siris and Roodman, 2008]. Sarcomas may present with worsening pain, lytic lesion on x-ray, fracture, a new mass, or rising SAP [Hansen *et al.* 2006]. The most common bones involved in pagetic osteosarcoma include pelvis, femur, humerus, tibia, and skull [Hansen *et al.* 2006]. Interestingly, despite being frequently involved by PDB, osteosarcoma is uncommon in the pagetic spine [Hansen *et al.* 2006]. Patients with pagetic sarcomas have a poor prognosis and most patients die from local extension of disease or pulmonary metastases within 3 years [Siris and Roodman, 2008]. A recent study reviewing all cases of pagetic sarcoma at the Royal Orthopaedic Hospital in Birmingham, UK, since 1975 [Mangham *et al.* 2009] suggested a declining incidence of sarcoma in PDB to about 0.3%. The mean age at presentation of sarcoma after 1996 was 76.6 years compared to 70.4 years in patients presenting before 1996, suggesting age at presentation may be increasing. The median survival remained poor at 0.66 years.

Skeletal or extraskeletal benign giant cell tumors or osteoclastomas [Singer and Mills, 1993; Ziambaras *et al.* 1997] have also been reported and appear to be corticosteroid responsive. There appears to be geographic clustering with many of these patients being descendents of four residents of Avellino, Italy [Rendina *et al.* 2004]. Finally, Peyronie's disease appears to be associated with PDB [Lyles *et al.* 1997].

Laboratory findings

The serum calcium and phosphorus are usually normal. In untreated patients, the serum total and bone specific alkaline phosphatase (BSAP) levels are usually elevated [Whyte, 2006]. In one study, the total SAP was elevated in 78% of PDB patients and BSAP elevated in 84% of PDB patients [Alvarez *et al.* 1995]. The elevation in total or BSAP reflects both the extent of the disease and the associated increased osteoblastic activity. The SAP may be normal in patients with minimal skeletal involvement or monostotic PDB, inactive disease, or after specific antipagetic treatment. The BSAP may be useful in these circumstances or when coexisting liver disease results in elevation of the SAP. Other markers of bone formation and bone resorption may also be elevated [Alvarez *et al.* 2001] but are expensive and usually not needed. The serum uric acid is sometimes elevated [Siris and Roodman, 2008] but gout has not been proven to occur more frequently in patients with PDB than the general population [Siris and Roodman, 2008]. Although hypercalcemia may complicate extensive PDB during periods of immobilization or dehydration, hypercalcemia usually reflects a coexisting condition such as primary hyperparathyroidism (PHPT). The presence of hypercalcemia should prompt an evaluation for an underlying cause and should not be assumed to be related to PDB. Hypercalciuria may occur due to increased bone resorption particularly with immobilization [Kanis, 1991b]. It is probably prudent to measure the serum 25-hydroxy vitamin D level to exclude vitamin D deficiency as a contributing factor to an elevated SAP. Furthermore, vitamin D deficiency should

always be corrected prior to initiating bisphosphonate therapy. The serum parathyroid hormone level may be elevated in a significant percentage (~15–20%) of patients with PDB [Siris *et al.* 1989, 1998]. In many of these patients, the elevation of parathyroid hormone is believed to represent secondary PHPT occurring at times of active pagetic bone formation. Secondary PHPT can also occur after suppression of bone resorption with bisphosphonate therapy [Siris *et al.* 1998]. Inadequate vitamin D stores and age-related declines in renal function could also contribute to secondary PHPT. PHPT may coexist with PDB, however, its prevalence is probably not more than expected [Gutteridge *et al.* 1999a]. Successful surgical treatment of PHPT may be followed by a significant decrease in SAP [Gutteridge *et al.* 1999a]. Because PHPT whether primary or secondary may have a negative impact on pagetic bone lesions, it is appropriate to treat secondary PHPT with adequate calcium and vitamin D and consider appropriate parathyroid surgery in the patient with coexistent PDB and PHPT [Brandi and Falchetti, 2006; Siris and Roodman, 2008].

Radiologic findings

A total body bone scan or a radiographic skeletal survey is often performed to assess the extent of disease. I prefer radionuclide bone scanning followed by targeted X-ray imaging of the bones that demonstrate abnormal radionuclide uptake. The enhanced skeletal uptake of radionuclide reflects increased bone formation and increased blood flow and may detect PDB before X-ray findings can be appreciated. Alternatively, some lesions in which osteoblastic activity has become inactive will be negative on bone scanning despite findings of PDB on plain radiographs. Treatment of PDB may render the radionuclide scan normal. On plain radiographs the earliest lesions are lytic due to increase osteoclastic activity. Lytic lesions may progress at a rate of about 1 cm yearly [Whyte, 2006]. The advancing lytic lesion may appear like a blade of grass or 'V-shaped lesion' in long bones and osteoporosis circumscripta in the skull [Cushing and Bone, 2002]. In response to increased bone resorption, bone formation is increased, resulting in a picture of mixed lytic and sclerotic areas. Bony enlargement, cortical thickening, increased trabecular pattern, and deformity or bowing may be seen. Skull involvement typically begins with radiolucent areas (osteoporosis circumscripta) followed by osteoblastic activity resulting in enlargement of the skull and a classic 'cotton wool' appearance [Cushing and Bone, 2002]. Involved vertebrae may have coarsened trabecular patterns and are sometimes osteosclerotic (ivory vertebra). The posterior elements are usually involved [Cushing and Bone, 2002]. Compression deformities may occur [Cushing and Bone, 2002]. Anterior, posterior, or lateral enlargement of verterbral bodies may be seen [Kanis, 1991a]. Radiographic examples are shown in Figure 2.

Nonspecific therapy

Acetaminophen, aspirin, or nonsteroidal anti-inflammatory drugs may be used for secondary degenerative joint disease [Siris and Roodman, 2008] and mild bone pain. Compensatory shoe lifts or orthotics may be useful in patients with bowed/shortened lower extremities and ambulation aids can be used as needed [Silverman, 2008]. Physical therapy is sometimes helpful.

Specific antipagetic drug treatment

Indications for specific antipagetic drug treatment

For the most part, indications are based on clinical experience rather than outcomes from clinical trials of significant size and duration. Clinically significant progressive deformity has been observed in untreated patients [Siris and Feldman, 1997]. Indications for treatment [Lyles *et al.* 2001; Siris *et al.* 2006; Silverman, 2008] are shown in Table 2 and include symptoms due to active PDB including bone pain at a pagetic site, fatigue fracture, headache from skull disease, or pain related to pagetic vertebrae. Neurologic symptoms due to spine or skull involvement are also indications for treatment. Patients with hearing loss due to temporal bone involvement should be treated in an attempt to prevent further hearing loss. Preoperative treatment is indicated in patients scheduled for elective surgery involving pagetic bone such as a total hip arthroplasty or tibial osteotomy in an attempt to decrease blood loss. Hypercalcemia related to immobilization in a patient with polyostotic PDB is another indication for treatment.

While treatment to prevent complications in asymptomatic patients seems reasonable, this remains an area of controversy. This includes treatment of patients with involvement adjacent to large joints to avoid arthritis, treatment of patients who may be at risk for bowing of long

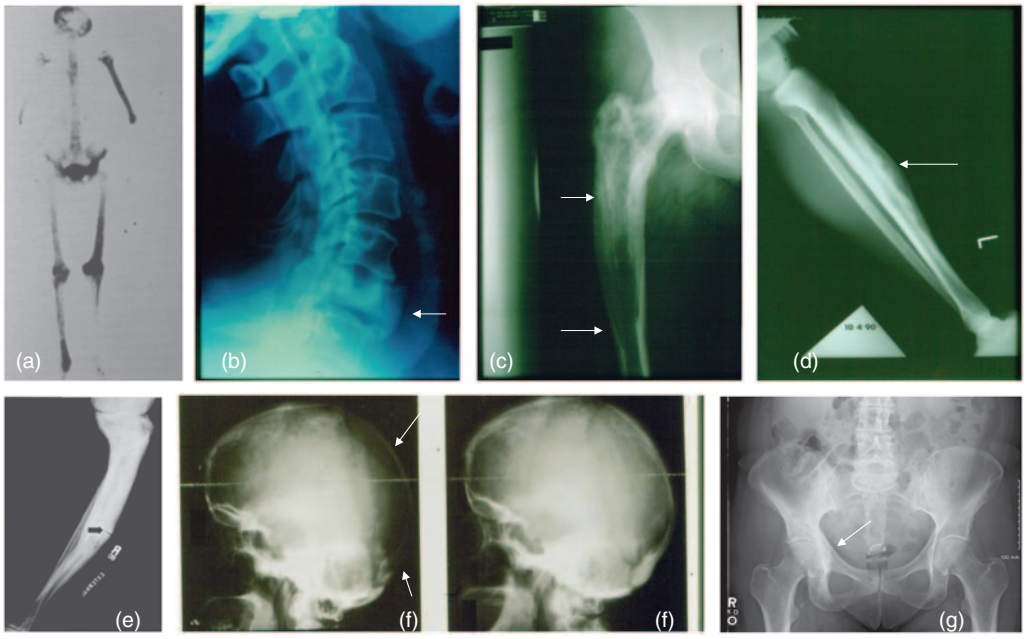

Figure 2. Radiographic appearance of Paget's disease of bone (PDB). (a) Bone scan in polyostotic PDB (with permission, courtesy of The Paget Foundation for Paget's Disease of Bone and Related Disorders). (b) Enlarged and osteosclerotic vertebral body. (c) Pagetic femur with osteosclerotic area proximal to a lytic front. (d) Lytic area in enlarged pagetic tibia. (e) Fissure fracture in a pagetic tibia (with permission, courtesy of The Paget Foundation for Paget's Disease of Bone and Related Disorders). (f) Lytic area in pagetic skull (osteoporosis circumscripta) with remineralization after aminobisphosphonate therapy. (g) PDB involving the right hemipelvis.

Table 2. Indications for specific antipagetic therapy.

Bone pain at a pagetic site
Neurologic symptoms
Pagetic hearing loss (treat to prevent further hearing loss)
Hypercalcemia
Before surgery on pagetic bone
High-output heart failure in a patient with extensive skeletal involvement
Prevention of progression/complications
Active Paget's disease of bone at sites such as skull, spine, weight-bearing long bones, adjacent to large joints, to prevent complications. This is controversial because it is not proven that treating such patients will prevent complications

bones, treatment of patients with temporal bone involvement to avoid hearing loss, and treatment of patients with significant skull or spine involvement to avoid neurologic problems.

Therapeutic options for specific antipagetic therapy

Table 3 lists the agents approved by the US Food and Drug Administration (FDA) for treatment of PDB. Specific antipagetic drugs inhibit osteoclastic activity. Salmon calcitonin has been available for many years. It is typically given a dose of 100 IU subcutaneously daily which is associated with an approximately 50% reduction in SAP and relief of some symptoms [Siris and Roodman, 2008]. Improved bone pain, healing of osteolytic lesions, and improvement in neurologic complications have been reported. The maintenance dose is often subsequently decreased to 50–100 IU three times weekly. This drug is less effective than the more potent bisphosphonates and resistance due to antibody formation against calcitonin may occur [Levy *et al.* 1988]. Side effects include nausea and flushing in some patients [Siris and Roodman, 2008]. Calcitonin is now used much less frequently than the more potent bisphosphonates and is primarily used in patients who cannot take or tolerate oral or intravenous (IV) bisphosphonate therapy. Nasal spray calcitonin is not FDA approved for PDB.

Bisphosphonates are nonbiodegradable synthetic analogs of inorganic pyrophosphate. These drugs adhere to mineralized surfaces, inhibit osteoclastic bone resorption (Figure 1) and have very long

Table 3. Drugs approved by the FDA for treatment of Paget's disease of bone.

Drug	Administration/dosage
Calcitonin (Miacalcin)	50–100 units by sc injection daily or three times weekly for 6–18 months
Etidronate (Didronel)	200–400 mg orally daily for 6 months; must be taken with 6–8 ounces of water on an empty stomach with no food, beverages, or medications for 2 hours before and after the dose; course should not exceed 6 months; repeat courses can be given after rest periods of 3–6 months.
Pamidronate (Aredia)	Approved regimen is 30 mg iv over 4 hours on 3 consecutive days. The drug is often used at 60 mg or 90 mg iv over 2–4 hours and repeated as clinically indicated. A single infusion is often effective in mild disease; two to three infusions may be required in more severe disease.
Alendronate (Fosamax)	40 mg orally daily for 6 months. Must be taken on an empty stomach with 6–8 ounces of water in the morning. Patient should wait at least 30 minutes before eating food or drinking anything other than water or taking a medication. Patient should not lie down for at least 30 minutes.
Tiludronate (Skelid)	400 mg orally daily for 3 months. Must be taken with 6–8 ounces of water on an empty stomach with no food, beverages, or medications for 2 hours before and after the dose.
Risedronate (Actonel)	30 mg orally daily for 2 months. Must be taken on an empty stomach with 6–8 ounces of water in the morning. Patient should wait at least 30 minutes before eating food or drinking anything other than water or taking a medication. Patient should not lie down for at least 30 minutes.
Zoledronic acid (Reclast)	5 mg iv over 15 minutes. The drug should not be used if the creatinine clearance is less than 35 ml/min. Patient should have adequate calcium and vitamin D to reduce the risk of hypocalcemia.

*Clodronate is not available in the US, but is available in some countries and is given 400–1600 mg daily orally for 3–6 months or 300 mg iv daily for 5 days.
iv, intravenous; sc, subcutaneous.

skeletal half-lives [Licata, 2005]. These drugs are often divided into two classes; simple bisphosphonates such as etidronate and tiludronate and the more potent nitrogen-containing bisphosphonates such as pamidronate, alendronate, risedronate, and zoledronic acid (ZA) [Licata, 2005]. The simple bisphosphonates appear to inhibit osteoclastic function by forming toxic analogues of ATP in osteoclasts [Frith *et al.* 2001]. Etidronate has been available for many years for treatment of PDB. For PDB, etidronate is typically given as 400 mg daily for 6 months followed by 6 months without therapy. This treatment results in approximately 50% reductions in SAP and SAP will normalize in approximately one in six patients [Siris *et al.* 1996; Miller *et al.* 1999]. Higher doses are not recommended because of the risk of a mineralization defect [Gibbs *et al.* 1986]. Tiludronate is another 'less potent' bisphosphonate. It is given in a dosage of 400 mg daily for 3 months. In one study, 35% of PDB patients achieved a normal SAP and 72% of patients had a decrease in SAP of at least 50% [McClung *et al.* 1995] with this regimen. Tiludronate appears to be somewhat more effective than etidronate for treatment of PDB [Roux *et al.* 1995].

The more potent amino bisphosphonates include alendronate, risedronate, pamidronate, and ZA, and are the preferred drugs. The potency of nitrogen-containing bisphosphonates in inhibiting osteoclastic bone resorption may be related to their ability to inhibit farnesyl diphosphate synthase [Dunford *et al.* 2001]. Alendronate and risedronate are given orally while pamidronate and ZA are given intravenously. In the treatment of PDB, alendronate is given at a dosage of 40 mg daily for 6 months. In a trial comparing alendronate to etidronate in the treatment of PDB, 63% of the patients treated with alendronate had normalization of SAP compared to 17% with etidronate [Siris *et al.* 1996]. A recently published trial compared alendronate 40 mg by tablet daily for 6 months with alendronate 280 mg in oral buffered solution once weekly for 6 months. Both drugs were equally effective in lowering SAP, however, the 280 mg oral buffer solution was associated with more gastrointestinal symptoms including nausea, abdominal pain, and diarrhea [Hooper *et al.* 2009]. Risedronate is given in a dosage of 30 mg daily for 2 months to treat PDB. In a pivotal trial of risedronate, 73% of PDB patients treated with risedronate normalized SAP compared to 15% of patients receiving etidronate [Miller *et al.* 1999]. A statistically significant reduction in pain was seen in the risedronate but not the etidronate group [Miller *et al.* 1999]. In a study of 13 patients with severe PDB (mean SAP 17 times the upper normal limit (UNL)) [Singer *et al.* 1998], there was a 77% decrease in SAP after an 8 week course of risedronate 30 mg daily. Ten patients had a second course of risedronate resulting in a mean 87% decrease in SAP. Pamidronate is FDA approved for PDB in a dosage of 30 mg intravenously over

4 hours on three consecutive days, however, other regimens are more commonly used [Siris, 1994]. Patients with mild disease may be treated with a single 60–90 mg infusion while patients with more severe disease may receive multiple 90 mg infusions. In a prospective, nonrandomized study [Tucci and Bontha, 2001] that evaluated the response of 80 PDB patients to IV pamidronate (180 mg over 3–6 weeks), the mean decrease in SAP was 63%. Normalization of SAP occurred in 86% of patients with a baseline SAP less than three times the UNL, 38% of patients with a baseline SAP three to six times the UNL, and 12% of patients with a baseline SAP more than six times the UNL [Tucci and Bontha, 2001]. In a study comparing oral risedronate (one or two courses of 30 mg daily for 8 weeks) to IV pamidronate (first course 30 mg three times; second course if needed 60 mg three times) in patients with acquired resistance to intravenous clodronate, 86% of risedronate-treated patients and 80% of pamidronate-treated patients achieved remission [Rendina *et al.* 2004]. Another study compared intravenous pamidronate to oral alendronate [Walsh *et al.* 2004]; 56% of patients treated with pamidronate and 86% of patients treated with alendronate achieved biochemical remission (normalization of SAP and urinary deoxypyridinoline to creatinine ratio). Remission rates in previously untreated patients were similar with pamidronate and alendronate, however, in patients previously treated with pamidronate the remission rate was higher with alendronate. Zoledronic acid was FDA approved for PDB in 2007. It is given in a dosage of 5 mg IV over 15–30 minutes. A study of patients with a mean baseline SAP of about four times normal was done comparing a single dose of ZA 5 mg IV to risedronate 30 mg by mouth daily for 60 days. At 6 months 89% of the patients treated with ZA and 58% of those treated with risedronate had normalized SAP [Reid *et al.* 2005]. In this study, SF-36 testing revealed that the ZA group had greater improvement in physical functioning at 3 months and general health at 6 months as compared to the risedronate group. In an 18 month extension of this study in patients who had had a therapeutic response defined as a normalization of SAP or a 75% or greater reduction in SAP, the SAP increased from 6 months to 24 months in the risedronate group but was stable in the ZA group, suggesting that the biochemical effect of ZA appears to be more durable than risedronate [Hosking *et al.* 2007]. Improvement in osteolytic lesions has been reported with amino-bisphosphonate therapy [Thiebaud *et al.* 1988; Reid *et al.* 1996; Brown *et al.* 2000; Walsh *et al.* 2004].

Acquired resistance to the biochemical response from etidronate, clodronate, and pamidronate has been reported [Rendina *et al.* 2004; Papapoulos *et al.* 2006]. This may be defined as an increase in the nadir SAP with subsequent treatments, requirement of a higher dose to get an equivalent response, and shortening of the length of time the patient remains in remission after a new course [Papapoulos *et al.* 2006]. These patients may respond well to an alternate bisphosphonate [Gutteridge *et al.* 1999b; Joshua *et al.* 2003; Rendina *et al.* 2004; Papapoulos *et al.* 2006].

In summary, when specific antipagetic therapy is needed, the amino bisphosphonates (alendronate, risedronate, pamidronate, and ZA) are first line therapy and provide both oral and intravenous options. Intravenous therapy may be preferred in patients with significant upper gastrointestinal problems or esophageal disease, patients in whom compliance to oral therapy is problematic, patients in whom a rapid antiresorptive effect is desired (e.g. neurologic symptoms or the urgent need for surgery on pagetic bone), or by patient preference. ZA appears to be the most potent drug and with the most sustained therapeutic effect for at least 2 years [Hosking *et al.* 2007].

Adverse effects of bisphosphonates have been reviewed recently [Kennel and Drake, 2009]. The major side effects of the oral amino bisphosphonates are esophageal and upper gastrointestinal symptoms [Kennel and Drake, 2009]. The most common side effect of intravenous pamidronate and ZA is a flu-like syndrome which occurs within a few days of treatment. In the ZA pivotal osteoporosis trial, this acute phase reaction occurred in 31.6% of patients after the first infusion, 6.6% of patients after the second infusion, and 2.8% of patients after the third infusion [Black *et al.* 2007]. This side effect can occur with oral bisphosphonates but is much less common. Use of acetaminophen may be useful in preventing these symptoms.

Severe musculoskeletal pain, attributed to bisphosphonate therapy, which may resolve slowly or incompletely after bisphosphonate

cessation has been reported [Wysowski and Chang, 2005]. All bisphosphonates list this potential side effect in their prescribing information and the FDA issued an alert about this issue in 2008 [US Food and Drug Adminstration, 2008a]. This complication appears to be rare.

Osteonecrosis of the jaw (ONJ) has been reported in patients treated with bisphosphonates [Woo *et al.* 2006]. Most of the cases have been in patients treated with high doses of intravenous bisphosphonates for malignancy and after tooth extraction [Woo *et al.* 2006]. This condition appears to be rare in patients treated with osteoporosis or PDB doses of bisphosphonates. ONJ has been estimated to occur in 1–10% of patients treated with IV bisphosphonates in cancer dosage regimens and about 1/10,000–<1/100,000 patient years in osteoporosis doses [Khosla *et al.* 2007]. The true incidence of ONJ in the treatment of nonmalignant bone diseases is unknown. It is appropriate to stress the importance of good dental hygiene and regular dental care prior to bisphosphonate therapy. If dental surgery is needed, it would be reasonable to delay initiation of bisphosphonate therapy until after the patient has had surgery and has healed. If dental surgery is needed while the patient is on bisphosphonate therapy, the dentist should be made aware of the bisphosphonate therapy. There is no evidence that stopping the bisphosphonate would be protective.

Mild hypocalcemia may occur especially after IV bisphosphonates, however, clinically significant hypocalcemia is unusual [Black *et al.* 2007]. Severe hypocalcemia following bisphosphonate therapy for PDB has, however, been reported [Whitson *et al.* 2006]. Patients treated with bisphosphonates for PDB should receive adequate calcium and vitamin D. A total calcium intake from diet and supplements in the range of 1500 mg daily is appropriate. A serum 25-hydroxy vitamin D level of greater than 30 ng/ml is considered adequate.

Atrial fibrillation has also been a concern with bisphosphonate therapy. In the HORIZON pivotal fracture trial for ZA, the treatment group had an increased incidence of serious atrial fibrillation [Black *et al.* 2007]. An analysis of the Fracture Intervention Trial (FIT) suggested increased atrial fibrillation with alendronate [Cummings *et al.* 2007] but another study did not confirm this finding [Sorensen *et al.* 2008]. An FDA statement released in November 2008 suggested that healthcare providers should not change their prescribing practices based on a possible association of bisphosphonate therapy with atrial fibrillation [US Food and Drug Adminstration, 2008b].

Twenty-three cases of esophageal cancer were recently reported in patients receiving alendronate from late 1995 to May 2008 by an FDA epidemiologist [Wysowski, 2009]. The median time of alendronate use to diagnosis was 2.1 years. There were also 31 patients from Europe and Japan with esophageal cancer who had received alendronate, risedronate, ibandronate, or etidronate [Wysowski, 2009]. Others have suggested that the incidence of esophageal cancer in bisphosphonate-treated patients is not greater than expected [Abrahamsen *et al.* 2009b; Solomon *et al.* 2009]. It is not clear whether esophageal cancer is increased patients receiving oral bisphosphonates or if certain populations of patients (e.g. pre-existing Barrett's esophagus) might be at greater risk from bisphosphonates. It seems prudent to avoid prescribing oral bisphosphonates to patients with Barrett's esophagus or other significant known esophageal disease [Kennel and Drake, 2009].

Atypical poorly-healing fractures with severe suppression of bone turnover as well as subtrochanteric femoral fractures have been reported in patients on long-term bisphosphonate therapy [Odvina *et al.* 2005; Kwek *et al.* 2008a, 2008b; Lenart *et al.* 2008, 2009; Goh *et al.* 2007; Visekruna *et al.* 2008; Edwards *et al.* 2009]. In the case of subtrochanteric femoral fractures, fracture may be preceded by pain and a stress fracture. These stress fractures are typically in the lateral aspect of the proximal femur, are associated with cortical thickening at the fracture site and may be bilateral. Some of these features are reminiscent of insufficiency fractures of PDB. It is not clear whether these uncommon fractures are an unusual osteoporotic fracture or caused by long-term bisphosphonate treatment [Abrahamsen *et al.* 2009b].

Ocular inflammation (iritis, uveitis, conjunctivitis, episcleritis, and scleritis) are rare side effects that can be seen with amino bisphosphonates. If iritis occurs, the drug should be stopped and ophthalmologic consultation obtained [Kennel and Drake, 2009]. Although amino bisphosphonates cannot be used in these patients,

non-nitrogen-containing bisphosphonates such as etidronate or tiludronate can be used [Siris and Roodman, 2008]. Synovitis, which may recur with rechallenge, has also been reported with aminobisphosphonate therapy [Jones *et al.* 2008].

Gallium nitrate and plicamycin (previously known as mithramycin) have been used in the past for PDB but are more toxic and not specifically FDA approved for this indication. These drugs are currently rarely used for PDB and are not generally recommended for this condition.

Denosumab is a monoclonal antibody to RANKL which is currently being studied for osteoporosis [Miller, 2009]. By inhibiting RANKL binding to RANK, this drug inhibits osteoclastic activity. It is not known if this drug will be effective for treatment of PDB.

The therapeutic biochemical target for antipagetic therapy is unclear. A 25% decrease in a biochemical marker such as SAP or BSAP may be considered to be a response [Selby *et al.* 2002]. Some authorities recommend normalization or near normalization of the SAP if this is possible [Siris, 1999; Papapoulos, 2002]. Patients are typically monitored with SAP or BSAP measurements every 3–6 months. Retreatment (at least 6 months after initial treatment) may be considered if the serum total or BSAP has increased 25% above the nadir value or if the patient develops recurrent symptoms [Siris, 1999]. Other authorities suggest retreatment only when patients have symptoms related to PDB as SAP levels appear to correlate poorly with quality of life [Langston *et al.* 2007]. Some patients with clinically significant and active PDB affecting small areas of the skeleton (e.g. monostotic disease of the tibia) may have normal biochemical markers of bone turnover. In this setting, repeat bone scanning may be useful in monitoring treatment.

Surgery

Surgery including fracture stabilization, corrective osteotomy and total joint arthroplasty is sometimes needed for patients with PDB [Parvizi *et al.* 2006]. Pagetic bone is very vascular [Rongstad *et al.* 1994] and it is recommended that patients receive specific antipagetic therapy prior to elective surgery on pagetic bone. Patients with PDB are at increased risk for heterotopic ossification after total hip arthroplasty and some authorities recommend preventive regimens with low dose radiation or pharmacologic agents in these patients. Patients with spinal involvement may have radiculopathy or myelopathy. This can be related to compressive spinal stenosis or 'vascular steal' resulting in reversible ischemia of the spinal cord. In this setting, aggressive antipagetic therapy is often effective, thus avoiding complicated surgery [Chen *et al.* 1979; Herzberg and Bayliss, 1980; Wallace *et al.* 1995; Bone, 2006]. When orthopedic surgery is needed on pagetic bone, it is best done by surgeons with previous experience in treating pagetic bone.

Patient followup

Patients who do not have indications for specific antipagetic therapy can be monitored with a yearly SAP or BSAP. Patients receiving active antipagetic therapy can be monitored with a SAP or BSAP every 3–6 months. It is reasonable to obtain radiographs of osteolytic lesions periodically, remembering that the lytic front typically advances approximately 1 cm annually.

Summary

PDB is a common condition, particularly in older persons of Northern European extraction. The incidence and severity of this condition may be decreasing. PDB is caused by accelerated osteoclastic bone resorption followed by increased bone formation in one or more bones resulting in skeletal lesions which can be osteolytic, mixed osteolytic/osteosclerotic, or osteosclerotic. Recently the SQSTM1 gene has been found to be one important cause of familial PDB. Symptoms and complications related to PDB can include bone pain, fracture, bone deformity, osteoarthritis, hearing loss, neurologic symptoms, cardiovascular complications, and, rarely, malignant transformation. Very effective medical therapy with potent aminobisphosphonates is available for patients requiring specific antipagetic treatment. Surgery is occasionally needed on pagetic bone and when possible should only be undertaken following effective medical therapy and by surgeons with significant experience treating this condition.

Additional information for patients and professionals

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Conflict of interest statement

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References

Abrahamsen, B., Eiken, P. and Eastell, R. (2009a) Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. *J Bone Miner Res* 24: 1095–1102.

Abrahamsen, B., Eiken, P. and Eastell, R. (2009b) More on reports of esophageal cancer with oral bisphosphonate use. *N Engl J Med* 360: 1789.

Altman, R.D. (1999) Arthritis in Paget's disease of bone. *J Bone Miner Res* 14(supplement 2): 85–87.

Altman, R.D. (2002) Epidemiology of Paget's disease of bone. *Clin Rev Bone Miner Metab* 1: 99–102.

Altman, R.D. and Collins, B. (1980) Musculoskeletal manifestations of Paget's disease of bone. *Arthritis Rheum* 23: 1121–1127.

Alvarez, L., Guanabens, N., Peris, P., Monegal, A., Bedini, J.L., Deulofeu, R. *et al.* (1995) Discriminative value of biochemical markers of bone turnover in assessing the activity of Paget's disease. *J Bone Miner Res* 10: 458–465.

Alvarez, L., Guanabens, N., Peris, P., Vidal, S., Ros, I., Monegal, A. *et al.* (2001) Usefulness of biochemical markers of bone turnover in assessing response to treatment of Paget's disease. *Bone* 29: 447–452.

Avramides, A. (1977) Salmon and porcine calcitonin treatment of Paget's disease of bone. *Clin Orthop Rel Res* 127: 78–85.

Basle, M.F., Fournier, J.G., Rozenblatt, S., Rebel, A. and Bouteille, M. (1986) Measles virus RNA Detected in Paget's disease bone tissue by *in situ* hybridization. *J Gen Virol* 67: 907–913.

Beyens, G., Daroszewska, A., de Freitas, F., Fransen, E., Vanhoenacker, F., Verbruggen, L. *et al.* (2007) Identification of sex-specific associations between polymorphisms of the osteoprotegerin gene, TNFRSF11B, and Paget's disease of bone. *J Bone Miner Res* 22: 1062–1071.

Birch, M.A., Taylor, W., Fraser, W.D., Ralston, S.H., Hart, C.A. and Gallagher, J.A. (1994) Absence of paramyxovirus RNA in cultures of Pagetic bone cells and in pagetic bone. *J Bone Miner Res* 9: 11–16.

Black, D.M., Delmas, P.D., Eastell, R., Reid, I.R., Boonen, S., Cauley, J.A. *et al.* (2007) Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 356: 1809–1822.

Bone, H.G. (2006) Nonmalignant complications of Paget's disease. *J Bone Miner Res* 21(supplement 2): P64–P68.

Boyle, W.J., Simonet, W.S. and Lacey, D.L. (2003) Osteoclast differentiation and activation. *Nature* 423: 337–342.

Brandi, M.L. and Falchetti, A. (2006) What is the relationship between Paget's disease of bone and hyperparathyroidism? *J Bone Miner Res* 21(supplement 2): P69–P74.

Brown, J.P., Chines, A.A., Myers, W.R., Eusebio, R.A., Ritter-Hrncirik, C. and Hayes, C.W. (2000) Improvement of Pagetic bone lesions with risedronate treatment: a radiologic study. *Bone* 26: 263–267.

Chamoux, E., Couture, J., Bisson, M., Morissette, J., Brown, J.P. and Roux, S. (2009) The p62 P392L mutation link to Paget's disease induces activation of human osteoclasts. *Molec Endocrinol* epub 9 July 2009.

Chen, J.R., Rhee, R.S.C., Wallach, S., Avramides, A. and Flores, A. (1979) Neurologic disturbances in Paget disease of bone: response to calcitonin. *Neurology* 29: 448–457.

Cody, J.D., Singer, F.R., Roodman, G.D., Otterund, B., Lewis, T.B., Leppert, M. *et al.* (1997) Genetic linkage of Paget disease of the bone to chromosome 18q. *Am J Hum Genet* 61: 1117–1122.

Cooper, C., Schafheutle, K., Dennison, E., Kellingray, S., Guyer, P. and Barker, D. (1999) The epidemiology of Paget's disease in Britain: is the prevalence decreasing? *J Bone Miner Res* 14: 192–197.

Cooper, C., Harvey, N.C., Dennison, E.M. and van Staa, T.P. (2006) Update on the epidemiology of Paget's disease of bone. *J Bone Miner Res* 21(supplement 2): P3–P8.

Cummings, S.R., Schwartz, A.V. and Black, D.M. (2007) Alendronate and atrial fibrillation. *N Engl J Med* 356: 1895–1896.

Cundy, T. (2006) Is the prevalence of Paget's disease of bone decreasing? *J Bone Miner Res* 21(supplement 2): P9–P13.

Cundy, T. and Bolland, M. (2008) Paget disease of bone. *Trends Endocrinol Metab* 19: 246–253.

Cundy, H.R., Gamble, G., Wattie, D., Rutland, M. and Cundy, T. (2004) Paget's disease of bone in New Zealand: continued decline in disease severity. *Calcif Tissue Int* 75: 358–364.

Cushing, F.R. and Bone, H.G. (2002) Radiographic diagnosis and laboratory evaluation of Paget's disease of bone. 1: 115–134.

Daroszewska, A., Hocking, L.J., McGuigan, F.E.A., Langdahl, B., Stone, M.D., Cundy, T. *et al.* (2004) Susceptibility to Paget's disease of bone is influenced by a common polymorphic variant of osteoprotegerin. *J Bone Miner Res* 19: 1506–1511.

Deftos, L.J. (2005) Treatment of Paget's disease – taming the wild osteoclast. *N Engl J Med* 353: 872–875.

Doyle, T., Gunn, J., Anderson, G., Gill, M. and Cundy, T. (2002) Paget's disease in New Zealand: evidence for declining prevalence. *Bone* 31: 616–619.

Dunford, J.E., Thompson, K., Coxon, F.P., Luckman, S.P., Hahn, F.M., Poulter, C.D. *et al.* (2001) Structure-activity relationships for inhibition of farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates. *J Pharm Exp Therap* 296: 235–242.

Edwards, M.H., McCrae, F.C. and Young-Min, S.A. (2009) Alendronate-related femoral diaphysis fracture – what should be done to predict and prevent subsequent fracture of the contralateral side? *Osteoporosis Int*. epub 27 June 2009.

Friedrichs, W.E., Reddy, S.V., Bruder, J.M., Cundy, T., Cornish, J., Singer, F.R. *et al.* (2002) Sequence analysis of measles virus nucleocapsid transcripts in patients with Paget's disease. *J Bone Miner Res* 17: 145–151.

Frith, J.C., Monkkonen, J., Auriola, S., Monkkonen, H. and Rogers, M.J. (2001) The molecular mechanism of action of the antiresorptive and antiinflammatory drug clodronate. *Arthritis Rheum* 44: 2201–2210.

Gennari, L., Di Stefano, M., Merlotti, D., Giordano, N., Martini, G., Tamone, C. *et al.* (2005) Prevalence of Paget's disease of bone in Italy. *J Bone Miner Res* 20: 1845–1850.

Gennari, L., Marlotti, D., Martini, G. and Nuti, R. (2006) Paget's disease of bone in Italy. *J Bone Miner Res* 21(supplement 2): P14–P21.

Gibbs, C.J., Aaron, J.E. and Peacock, M. (1986) Osteomalacia in Paget's disease treated with short term, high dose sodium etidronate. *Br Med J* 292: 1227–1229.

Goh, S.K., Yang, K.Y., Koh, J.S.B., Wong, M.K., Chua, S.Y., Chua, D.T.C. *et al.* (2007) Subtrochanteric insufficiency fractures in patients on alendronate therapy. *J Bone Joint Surg* 89–B: 349–353.

Gold, D.T., Boisture, J., Shipp, K.M., Pieper, C.F. and Lyles, K. (1996) Paget's disease of bone and quality of life. *J Bone Miner Res* 11: 1897–1903.

Good, D.A., Busfield, F., Fletcher, B.H., Duffy, D.L., Kesting, J.B., Anderson, J. *et al.* (2002) Linkage of Paget disease of bone to a novel region on human chromosome 18q23. *Am J Hum Genet* 70: 517–525.

Good, D.A., Busfield, F., Fletcher, B.H., Lovelock, P.K., Duffy, D.L., Kesting, J.B. *et al.* (2004) Identification of SQSTM1 mutations in familial Paget's disease in Australian pedigrees. *Bone* 35: 277–282.

Gordon, M.T., Anderson, D.C. and Sharpe, P.T. (1991) Canine distemper virus localised in bone cells of patients with Paget's disease. *Bone* 12: 195–201.

Gordon, M.T., Mee, A.P., Anderson, D.C. and Sharpe, P.T. (1992) Canine distemper virus transcripts sequenced from Pagetic bone. *Bone Miner* 19: 159–174.

Guanabens, N., Garrido, J., Gobbo, M., Morales Piga, A., del Pino, J., Torrijos, A. *et al.* (2008) Prevalence of Paget's disease of bone in Spain. *Bone* 43: 1006–1009.

Gutteridge, D.H., Gruber, H.E., Kermode, D.G. and Worth, G.K. (1999a) Thirty cases of concurrent Paget's disease and primary hyperparathyroidism: sex distribution, histomorphometry, and prediction of the skeletal response to parathyroidectomy. *Calcif Tissue Int* 65: 427–435.

Gutteridge, D.H., Ward, L.C., Stewart, G.O., Retallack, R.W., Will, R.K., Prince, R.L. *et al.* (1999b) Paget's disease: acquired resistance to one aminobisphosphonate with retained response to another. *J Bone Miner Res* 14(supplement 2): 79–84.

Hansen, M.F., Seton, M. and Merchant, A. (2006) Osteosarcoma in Paget's disease of bone. *J Bone Miner Res* 21(supplement 2): P58–P63.

Haslam, S.I., Van Hul, W., Morales-Piga, A., Balemans, W., San-Millan, J.L., Nakatsuka, K. *et al.* (1998) Paget's disease of bone: evidence for a susceptibility locus on chromosome 18q and for genetic heterogeneity. *J Bone Miner Res* 13: 911–917.

Helfrich, M.H., Hobson, R.P., Grabowski, P.S., Zurbriggen, A., Cosby, S.L., Dickson, G.R. *et al.* (2000) A negative search for a paramyxoviral etiology of Paget's disease of bone: molecular, immunological, and ultrastructural studies in U.K. patients. *J Bone Miner Res* 15: 2315–2329.

Herzberg, L. and Bayliss, E. (1980) Spinal-cord syndrome due to non-compressive Paget's disease of bone: a spinal-artery steal phenomenon reversible with calcitonin. *Lancet* 2(2184): 13–15.

Hiruma, Y., Kurihara, N., Subler, M.A., Zhou, H., Boykin, C.S., Zhang, H. *et al.* (2008) A SQSTM1/p62 mutation linked to Paget's disease increases the osteoclastogenic potential of the bone microenvironment. *Hum Molec Genet* 17: 3708–3719.

Hocking, L.J., Herbert, C.A., Nicholls, R.K., Williams, F., Bennett, S.T., Cundy, T. *et al.* (2001) Genomewide search in familial Paget disease of bone shows evidence of genetic heterogeneity with candidate loci on chromosomes 2q36, 10p13, and 5q35. *Am J Hum Genet* 69: 1055–1061.

Hocking, L.J., Lucas, G.J.A., Daroszewska, A., Mangion, J., Olavesen, M., Cundy, T. *et al.* (2002) Domain-specific mutations in sequestosome 1 (SQSTM1) cause familial and sporadic Paget's disease. *Hum Mol Genet* 11: 2735–2739.

Holdaway, I.M., Ibbertson, H.K., Wattie, D., Scragg, R. and Graham, P. (1990) Previous pet ownership and Paget's disease. *Bone Miner* 8: 53–58.

Hooper, M., Faustino, A., Reid, I.R., Hosking, D., Gilchrist, N.L., Selby, P. *et al.* (2009) Randomized, active-controlled study of once-weekly alendronate 280 mg high dose oral buffered solution for treatment of Paget's disease. *Osteoporosis Int* 20: 141–150.

Hosking, D., Lyles, K., Brown, J.P., Fraser, W.D., Miller, P., Curiel, M.D. *et al.* (2007) Long-term control of bone turnover in Paget's disease with zoledronic acid and risedronate. *J Bone Miner Res* 22: 142–148.

Hoyland, J.A., Freemont, A.J. and Sharpe, P.T. (1994) Interleukin-6, IL-6 receptor, and IL-6 nuclear factor gene expression in Paget's disease. *J Bone Miner Res* 9: 75–80.

Hughes, A.E., Ralston, S.H., Marken, J., Bell, C., MacPherson, H., Wallace, R.G.H. *et al.* (2000) Mutations in TNFRSF11A, affecting the signal peptide of RANK, cause familial expansile osteolysis. *Nature Genetics* 24: 45–48.

Hultgren, H. (1998) Osteitis deformans (Paget's disease) and calcific disease of the heart valves. *Am J Cardiol* 81: 1461–1464.

Jones, D.P.G., Savage, R.L. and Highton, J. (2008) Alenodronate-induced synovitis. *J Rheumatol* 35: 537–538.

Joshua, F., Epstein, M. and Major, G. (2003) Bisphosphonate resistance in Paget's disease of bone. *Arthritis Rheum* 48: 2321–2323.

Kanis, J.A. (1991a) Radiological features. In: Kanis, J.A. (ed.), Pathophysiology and treatment of Paget's disease of bone, Carolina Academic Press/Martin Dunitz, 41–88.

Kanis, J.A. (1991b) Biochemical and endocrine aspects of Paget's disease. In: Kanis, J.A. (ed.), Pathophysiology and treatment of Paget's disease of bone, Carolina Academic Press/Martin Dunitz, 89–109.

Kennel, K.A. and Drake, M.T. (2009) Adverse effects of bisphosphonates: implications for osteoporosis management. *Mayo Clin Proc* 84: 632–638.

Khan, S.A., Brennan, P., Newman, J., Gray, R.E.S., McCloskey, E.V. and Kanis, J.A. (1996) Paget's disease of bone and unvaccinated dogs. *Bone* 19: 47–50.

Khosla, S., Burr, D., Cauley, J., Dempster, D.W., Ebeling, P.R., Felsenberg, D. *et al.* (2007) Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 22: 1479–1491.

Kimonis, V.E. and Watts, G.D.J. (2005) Autosomal dominant inclusion body myopathy, Paget disease of bone, and frontotemporal dementia. *Alzheimer Dis Assoc Disord* 19(supplement 1): S44–S47.

Kurihara, N., Reddy, S.V., Menaa, C., Anderson, D. and Roodman, G.D. (2000) Osteoclasts expressing the measles virus nucleocapsid gene display a pagetic phenotype. *J Clin Invest* 105: 607–614.

Kurihara, N., Zhou, H., Reddy, S.V., Garcia Palacios, V., Subler, M.A., Dempster, D.W. *et al.* (2006) Experimental models of Paget's disease. *J Bone Miner Res* 21(supplement 2): P55–P57.

Kwek, E.B.K., Koh, J.S.B. and Howe, T.S. (2008a) More on atypical fractures of the femoral diaphysis. *N Engl J Med* 359: 316–317.

Kwek, E.B.K., Goh, S.K., Koh, J.S.B., Png, M.A. and How, T.S. (2008b) An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? *Injury* 39: 224–231.

Langston, A.L., Campbell, M.K., Fraser, W.D., MacLennan, G., Selby, P., Ralston, S.H. *et al.* (2007) Clinical determinants of quality of life in Paget's disease of bone. *Calcif Tissue Int* 80: 1–9.

Laroche, M. and Delmotte, A. (2005) Increased arterial calcification in Paget's disease of bone. *Calcif Tissue Int* 77: 129–133.

Laurin, N., Brown, J.P., Lemainque, A., Duchesne, A., Huot, D., Lacourciere, Y. *et al.* (2001) Paget disease of bone: mapping of two loci at 5135-qter and 5131. *Am J Hum Genet* 69: 528–543.

Laurin, N., Brown, J.P., Morissette, J. and Raymond, V. (2002) Recurrent mutation of the gene encoding sequestosome 1 (SQSTM1/p62) in Paget disease of bone. *Am J Hum Genet* 70: 1582–1588.

Leach, R.J., Singer, F.R., Ench, Y., Wisdom, J.H., Pina, D.S. and Johnson-Pais, T.L. (2006) Clinical and cellular phenotypes associated with *sequestosome 1 (SQSTM1)* mutations. *J Bone Miner Res* 21(supplement 2): P45–P50.

Lenart, B.A., Lorich, D.G. and Lane, J.M. (2008) Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. *N Engl J Med* 358: 1304–1305.

Lenart, B.A., Neviaser, A.S., Lyman, S., Chang, C.C., Edobor-Osula, F., Steele, B. *et al.* (2009) Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. *Osteoporosis Int* 20: 1353–1362.

Lever, J.H. (2002) Paget's disease of bone in Lancashire and arsenic pesticide in cotton mill wastewater: a speculative hypothesis. *Bone* 31: 434–436.

Levy, F., Muff, R., Dotti-Sigrist, S., Dambacher, A. and Fischer, J.A. (1988) Formation of neutralizing antibodies during intranasal synthetic salmon calcitonin treatment of Paget's disease. *J Clin Endocrinol Metab* 67: 541–545.

Licata, A. (2005) Discovery, clinical development, and therapeutic uses of bisphosphonates. *Ann Pharmacother* 39: 668–677.

Lopez-Abente, G., Morales-Piga, A., Elena-Ibanez, A., Rey-Rey, J.S. and Corres-Gonzalez, J. (1997)

Cattle, pets, and Paget's disease of bone. *Epidemiology* 8: 247–251.

Lucas, G.J.A., Daroszewska, A. and Ralston, S.H. (2006a) Contribution of genetic factors to the pathogenesis of Paget's disease of bone and related disorders. *J Bone Miner Res* 21(supplement 2): P31–P37.

Lucas, G.J.A., Mehta, S.G., Hocking, L.J., Stewart, T.L., Cundy, T., Nicholson, G.C. *et al.* (2006b) Evaluation of the role of valosin-containing protein in the pathogenesis of familial and sporadic Paget's disease of bone. *Bone* 38: 280–285.

Lucas, G.J.A., Riches, P.L., Hocking, L.J., Cundy, T., Nicholson, G.C., Walsh, J.P. *et al.* (2008) Identification of a major locus for Paget's disease on chromosome 10p13 in families of British descent. *J Bone Miner Res* 23: 58–63.

Lyles, K.W., Gold, D.T., Newton, R.A., Parekh, S., Shipp, K.M., Pieper, C.F. *et al.* (1997) Peyronie's disease is associated with Paget's disease of bone. *J Bone Miner Res* 12: 929–934.

Lyles, K.W., Siris, E.S., Singer, F.R. and Meunier, P.J. (2001) A clinical approach to diagnosis and management of Paget's disease of bone. *J Bone Miner Res* 16: 1379–1387.

Mangham, D.C., Davie, M.W. and Grimer, R.J. (2009) Sarcoma arising in Paget's disease of bone: declining incidence and increasing age at presentation. *Bone* 44: 431–436.

Martini, G., Gennari, L., Merlotti, D., Salvadori, S., Franci, M.B., Campagna, S. *et al.* (2007) Serum OPG and RANKL levels before and after intravenous bisphosphonate treatment in Paget's disease of bone. *Bone* 40: 457–463.

Matthews, B.G., Naot, D., Bava, U., Callon, K.E., Pitto, R.P., McCowan, S.A. *et al.* (2009) Absence of somatic SQSTM1 mutations in Paget's disease of bone. *J Clin Endocrinol Metab* 94: 691–694.

McCloskey, E.V. and Kanis, J.A. (2002) Neurological complications of Paget's disease. *Clin Rev Bone Miner Metab* 1: 135–143.

McClung, M.R., Tou, C.K.P., Goldstein, N.H. and Picot, C. (1995) Tiludronate therapy for Paget's disease of bone. *Bone* 17: 493S–496S.

Mee, A.P., May, C., Bennett, D. and Sharpe, P.T. (1995) Generation of multinucleated osteoclast-like cells from canine bone marrow: effects of canine distemper virus. *Bone* 17: 47–55.

Mee, A.P., Dixon, J.A., Hoyland, J.A., Davies, M., Selby, P.L. and Mawer, E.B. (1998) Detection of canine distemper virus in 100% of Paget's disease samples by in situ-reverse transcriptase-polymerase chain reaction. *Bone* 23: 171–175.

Menaa, C., Reddy, S.V., Kurihara, N., Maeda, H., Anderson, D., Cundy, T. *et al.* (2000) Enhanced RANK ligand expression and responsivity of bone marrow cells in Paget's disease of bone. *J Clin Invest* 105: 1833–1838.

Merchant, A., Smielewska, M., Patel, N., Akunowicz, J.D., Saria, E.A., Delaney, J.D. *et al.* (2009) Somatic mutations in SQSTM1 detected in affected tissues from patients with sporadic Paget's disease of bone. *J Bone Miner Res* 24: 484–494.

Miller, P.D. (2009) Denosumab: anti-RANKL antibody. *Curr Osteoporos Rep* 7: 18–22.

Miller, P.D., Brown, J.P., Siris, E.S., Hoseyni, M.S., Axelrod, D.W., Bekker, P.J. *et al.* (1999) A randomized, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. *Am J Med* 106: 513–520.

Mills, B.G. and Singer, F.R. (1976) Nuclear inclusions in Paget's disease of bone. *Science* 194: 201–202.

Monsell, E.M. (2004) The mechanism of hearing loss in Paget's disease of bone. *Laryngoscope* 114: 598–606.

Monsell, E.M., Cody, D.D., Bone, H.G. and Divine, G.W. (1999) Hearing loss as a complication of Paget's disease of bone. *J Bone Miner Res* 14(supplement 2): 92–95.

Morales-Piga, A.A., Moya, J.L., Bachiller, F.J., Munoz-Malo, M.T., Benavides, J. and Abraira.V (2000) Assessment of cardiac function by echocardiography in Paget's disease of bone. *Clin Exper Rheum* 18: 31–37.

Nakatsuka, K., Nishizawa, Y. and Ralson, S.H. (2003) Phenotypic characterization of early onset Paget's disease of bone caused by a 27-bp duplication in the TNFRSF11A gene. *J Bone Miner Res* 18: 1381–1385.

O'Driscoll, J.B. and Anderson, D.C. (1985) Past pets and Paget's disease. *Lancet* 2(8461): 919–921.

Odvina, C.V., Zerwekh, J.E., Rao, S., Maalouf, N., Gottschalk, F.A. and Pak, C.Y.C. (2005) Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab* 90: 1294–1301.

Ooi, C.G., Walsh, C.A., Gallagher, J.A. and Fraser, W.D. (2000) Absence of measles virus and canine distemper virus transcripts in long-term bone marrow cultures from patients with Paget's disease of bone. *Bone* 27: 417–421.

Paget, J. (1877) On a form of chronic inflammation of bone (osteitis deformans). *Medico-Chir Trans* 60: 29–53.

Pane, A. (2007) Paget disease manifesting with compressive sixth-nerve palsy that resolved with intravenous zoledronic acid therapy. *Arch Ophthalmol* 125: 1440–1441.

Papapoulos, S.E. (2002) Pharmacological management of Paget's disease of bone. *Clin Rev Bone Miner Metab* 1: 149–157.

Papapoulos, S.E., Eckhoff, E.M.W. and Zwinderman, A.H. (2006) Acquired resistance to bisphosphonates in Paget's disease of bone. *J Bone Miner Res* 21(supplement 2): P88–P91.

Parvizi, J., Klein, G.R. and Sim, F.H. (2006) Surgical management of Paget's disease of bone. *J Bone Miner Res* 21(supplement 2): P75–P82.

Poncelet, A. (1999) The neurologic complications of Paget's disease. *J Bone Miner Res* 14(supplement 2): 88–91.

Ralston, S.H. (2008) Pathogenesis of Paget's disease of bone. *Bone* 43: 819–825.

Ralston, S.H., Digiovine, F.S., Gallacher, S.J., Boyle, I.T. and Duff, G.W. (1991) Failure to detect paramyxovirus sequences in Paget's disease of bone using the polymerase chain reaction. *J Bone Miner Res* 6: 1243–1248.

Ralston, S.H., Afzal, M.A., Helfrich, M.H., Fraser, W.D., Gallagher, J.A., Mee, A. *et al.* (2007) Multicenter blinded analysis of RT-PCR detection methods for paramyxoviruses in relation to Paget's disease of bone. *J Bone Miner Res* 22: 569–577.

Ralston, S.H., Langston, A.L. and Reid, I.R. (2008) Pathogenesis and management of Paget's disease of bone. *Lancet* 372: 155–163.

Redden, J.F., Dixon, J., Vennart, W. and Hosking, D.J. (1981) Management of fissure fractures in Paget's disease. *Int Orthop* 5: 103–106.

Reddy, S.V., Singer, F.R. and Roodman, G.D. (1995) Bone marrow mononuclear cells from patients with Paget's disease contain measles virus nucleocapsid messenger ribonucleic acid that has mutations in a specific region of the sequence. *J Clin Endocrinol Metab* 80: 2108–2111.

Reddy, S.V., Singer, F.R., Mallette, L. and Roodman, G.D. (1996) Detection of measles virus nucleocapsid transcripts in circulating blood cells from patients with Paget disease. *J Bone Miner Res* 11: 1602–1607.

Reid, I.R., Nicholson, G.C., Weinstein, R.S., Hosking, D.J., Cundy, T., Kotowicz, M.A. *et al.* (1996) Biochemical and radiologic improvement in Paget's disease of bone treated with alendronate: a randomized, placebo-controlled trial. *Am J Med* 17: 341–348.

Reid, I.R., Miller, P., Lyles, K., Fraser, W., Brown, J.P., Saidi, Y. *et al.* (2005) Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. *N Engl J Med* 353: 898–908.

Rendina, D., Mossetti, G., Soscia, E., Sirignano, C., Insabato, L., Viceconti, R. *et al.* (2002) Giant cell tumor and Paget's disease of bone in one family. *Clin Orthop* 421: 218–224.

Rendina, D., Mossetti, G., Viceconti, R., Sorrentino, M. and Nunziata.V (2004) Risedronate and pamidronate treatment in the clinical management of patients with severe Paget's disease of bone and acquired resistance to bisphosphonates. *Calcif Tissue Int* 75: 189–196.

Rendina, D., Gennari, L., De Filippo, G., Merlotti, D., de Campora, E., Fazioli, F. *et al.* (2006) Evidence for increased clinical severity of familial and sporadic Paget's disease of bone in Campania, Southern Italy. *J Bone Miner Res* 21: 1828–1835.

Rhodes, E.C., Johnson-Pais, T.L., Singer, F.R., Ankerts, D.P., Bruder, J.M., Wisdom, J. *et al.* (2008) Sequestosome 1 (SQSTM1) mutations in Paget's disease of bone from the United States. *Calcif Tissue Int* 82: 271–277.

Rogers, J., Jeffrey, D.R. and Watt.I (2002) Paget's disease in an archeological population. *J Bone Miner Res* 17: 1127–1134.

Rongstad, K.M., Wheeler, D.L. and Enneking, W.F. (1994) A comparison of the amount of vascularity in Pagetic and normal human bone. *Clin Orthop* 306: 247–249.

Roodman, G.D. (1996) Paget's disease and osteoclast biology. *Bone* 19: 209–212.

Roodman, G.D. and Windle, J.J. (2005) Paget disease of bone. *J Clin Invest* 115: 200–208.

Roodman, G.D., Kurihara, N., Ohsaki, Y., Kukita, A., Hosking, D., Demulder, A. *et al.* (1992) Interleukin 6: a potential autocrine/paracrine factor in Paget's disease of bone. *J Clin Invest* 89: 46–52.

Roux, C., Gennari, C., Farrerons, J., Devogelaer, J.P., Mulder, H., Kruse, H.P. *et al.* (1995) Comparative prospective, double-blind, multicenter study of the efficacy of tiludronate and etidronate in the treatment of Paget's disease of bone. *Arthritis Rheum* 38: 851–858.

Rubin, D.J. and Levin, R.M. (2009) Neurologic complications of Paget disease of bone. *Endocr Pract* 15: 158–166.

Schmidek, H.H. (1977) Neurologic and neurosurgical sequelae of Paget's disease of bone. *Clin Orthop Rel Res* 127: 70–77.

Selby, P.L., Davie, M.W.J., Ralston, S.H. and Stone, M.D. (2002) Guidelines on the management of Paget's disease of bone. *Bone* 31: 366–373.

Selby, P.L., Davies, M. and Mee, A.P. (2006) Canine distemper virus induces human osteoclastogenesis through NF-κB and sequestosome 1/P62 activation. *J Bone Miner Res* 21: 1750–1756.

Seton, M., Choi, H.K., Hansen, M.F., Sebaldt, R.J. and Cooper, C. (2003) Analysis of environmental factors in familial versus sporadic Paget's disease of bone – the New England registry for Paget's disease of bone. *J Bone Miner Res* 18: 1519–1524.

Silverman, S.L. (2008) Paget disease of bone: therapeutic options. *J Clin Rheumatol* 14: 299–305.

Singer, F.R. (1977) Human calcitonin treatment of Paget's disease of bone. *Clin Orthop Rel Res* 127: 86–93.

Singer, F.R. and Mills, B.G. (1993) Giant cell tumor arising in Paget's disease of bone. *Clin Orthop* 293: 293–301.

Singer, F.R., Clemens, T.L., Eusebio, R.A. and Bekker, P.J. (1998) Risedronate, a highly effective oral agent in the treatment of patients with severe Paget's disease. *J Clin Endocrinol Metab* 83: 1906–1910.

Singer, F.R., Mills, B.G., Gruber, H.E., Windle, J.J. and Roodman, G.D. (2006) Ultrastructure of bone cells in Paget's disease of bone. *J Bone Miner Res* 21(supplement 2): P51–P54.

Siris, E. (1991) Indications for medical treatment of Paget's disease of bone. In: Singer, F.R. and Wallach, S. (eds), Paget's disease of bone: clinical assessment, present and future therapy, Elsevier.

Siris, E. (1994) Perspectives: a practical guide to the use of pamidronate in the treatment of Paget's disease. *J Bone Miner Res* 9: 303–304.

Siris, E.S. (1999) Goals of treatment for Paget's disease of bone. *J Bone Miner Res* 14(supplement 2): 49–52.

Siris, E. and Feldman, F. (1997) Clinical vignette: natural history of untreated Paget's disease of the tibia. *J Bone Miner Res* 12: 691–692.

Siris, E. and Roodman, G.D. (2008) Paget's disease of bone. In: Rosen, C.J., Compston, J.E. and Lian, J.B. (eds), Primer on the metabolic bone diseases and disorders of mineral metabolism, 7th edition. American Society for Bone and Mineral Research, 335–343.

Siris, E., Clemens, T.P., McMahon, D., Gordon, A., Jacobs, T.P. and Canfield, R.E. (1989) Parathyroid function in Paget's disease of bone. *J Bone Miner Res* 4: 75–79.

Siris, E., Kelsey, J.L., Flaster, E. and Parker, S. (1990) Paget's disease of bone and previous pet ownership in the United States: dogs exonerated. *Int J Epidemiol* 19: 455–458.

Siris, E.S., Ottman, R., Flaster, E. and Kelsey, J.L. (1991) Familial aggregation of Paget's disease of bone. *J Bone Miner Res* 6: 495–500.

Siris, E., Weinstein, R.S., Altman, R., Conte, J.M., Favus, M., Lombardi, A. *et al.* (1996) Comparative study of alendronate versus etidronate for the treatment of Paget's disease of bone. *J Clin Endocrinol Metab* 81: 961–967.

Siris, E.S., Chines, A.A., Altman, R.D., Brown, J.P., Johnston Jr, C.C., Lang, R. *et al.* (1998) Risedronate in the treatment of Paget's disease of bone: an open label, multicenter study. *J Bone Miner Res* 13: 1032–1038.

Siris, E.S., Lyles, K.W., Singer, F.R. and Meunier, P.J. (2006) Medical management of Paget's disease of bone: indications for treatment and review of current therapies. *J Bone Miner Res* 21(supplement 2): P94–P98.

Solomon, D., Patrick, A. and Brookhart, M.A. (2009) More on reports of esophageal cancer with oral bisphosphonate use. *N Engl J Med* 360: 1789–1790.

Sorensen, H.T., Christensen, S., Mehnert, F., Pedersen, L., Chapurlat, R.D., Cummings, S.R. *et al.* (2008) Use of bisphosphonates among women and risk of atrial fibrillation and flutter: population base case-control study. *BMJ* 336: 813–816.

Strickberger, S.A., Schulman, S.P. and Hutchins, G.M. (1987) Association of Paget's disease of bone with calcific aortic valve disease. *Am J Med* 82: 953–956.

Thiebaud, D., Jaeger, P., Gobelet, C., Jacquet, A.F. and Burckhardt, P. (1988) A single infusion of the bisphosphonate AHPrBP (APD) as treatment of Paget's disease of bone. *Am J Med* 85: 207–212.

Tiegs, R.D., Lohse, C.M., Wollan, P.C. and Melton, L.J. (2000) Long-term trends in the incidence of Paget's disease of bone. *Bone* 27: 423–427.

Tilyard, M.W., Gardner, R.J.M., Milligan, L., Cleary, T.A. and Stewart, R.D.H. (1982) A probable linkage between familial Paget's disease and the HLA Loci*. *Aust N. Z. J Med* 12: 498–500.

Tucci, J.R. and Bontha, S. (2001) Intravenously administered pamidronate in the treatment of Paget's disease of bone. *Endocr Pract* 7: 423–429.

US Food and Drug Administration (2008a) Bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa).

US Food and Drug Administration (2008b) Bisphosphonates marketed as Alendronate (Fosamax, Fosamax Plus D), Etidronate (Didronel), Ibandronate (Boniva), Pamidronate (Aredia), Risedronate (Actonel, Actonel w/Calcium), Tiludronate (Skelid), and Zoledronic acid (Reclast, Zometa).

Viassolo, V., Previtali, S.C., Schiatti, E., Magnani, G., Minetti, C., Zara, F. *et al.* (2008) Inclusion body myopathy, Paget's disease of the bone and frontotemporal dementia: recurrence of the VCP R155 H mutation in an Italian family and implications for genetic counselling. *Clin Genet* 74: 54–60.

Visekruna, M., Wilson, D. and McKiernan, F.E. (2008) Severely suppressed bone turnover and atypical skeletal fragility. *J Clin Endocrinol Metab* 93: 2948–2952.

Wallace, E., Wong, J. and Reid, I.R. (1995) Pamidronate treatment of the neurologic sequelae of Pagetic spinal stenosis. *Arch Intern Med* 155: 1813–1815.

Walsh, J.P., Ward, L.C., Stewart, G.O., Will, R.K., Criddle, R.A., Prince, R.L. *et al.* (2004) A randomized clinical trial comparing oral alendronate and intravenous pamidronate for the treatment of Paget's disease of bone. *Bone* 34: 747–754.

Watts, G.D.J., Wymer, J., Kovach, M.J., Mehta, S.G., Mumm, S., Darvish, D. *et al.* (2004) Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. *Nature Genetics* 36: 377–381.

Watts, G.D.J., Thomasova, D., Ramdeen, S.K., Fulchiero, E.C., Mehta, S.G., Drachman, D.A. *et al.* (2007) Novel VCP mutations in inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia. *Clin Genet* 72: 420–426.

Wermers, R.A., Tiegs, R.D., Atkinson, E.J., Achenbach, S.J. and Melton III, L.J. (2008) Morbidity and mortality associated with Paget's disease of bone: a population-based study. *J Bone Miner Res* 23: 819–825.

Whitson, H.E., Lobaugh, B. and Lyles, K.W. (2006) Severe hypocalcemia following bisphosphonate treatment in a patient with Paget's disease of bone. *Bone* 39: 954–958.

Whyte, M.P. (2006) Paget's disease of bone. *N Engl J Med* 355: 593–600.

Whyte, M.P. and Hughes, A.E. (2002) Expansile skeletal hyperphosphatasia is caused by a 15-base pair tandem duplication in TNFRSF11A encoding RANK and is allelic to familial expansile osteolysis. *J Bone Miner Res* 17: 26–29.

Whyte, M.P., Obrecht, S.E., Finnegan, P.M., Jones, J.L., Podgornik, M.N., McAlister, W.H. *et al.* (2002) Osteoprotegerin deficiency and juvenile Paget's disease. *N Engl J Med* 347: 175–184.

Wirfel, K.L., Bruder, J.M., Vardag, A. and Roodman, G.D. (1999) Osteoclast function in healthy subjects and in patients with Paget's disease. *Endocrinologist* 9: 263–269.

Woo, S.B., Hellstein, J.W. and Kalmar, J.R. (2006) Systematic review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 144: 753–761.

Wuyts, W., Wesenbeeck, L.V., Morales-Piga, A., Ralston, S., Hocking, L., Vanhoenacker, F. *et al.* (2001) Evaluation of the role of RANK and OPG genes in Paget's disease of bone. *Bone* 28: 104–107.

Wysowski, D.K. (2009) Reports of esophageal cancer with oral bisphosphonate use. *N Engl J Med* 360: 89–90.

Wysowski, D.K. and Chang, J.T. (2005) Alendronate and risedronate: reports of severe bone, joint, and muscle pain. *Arch Intern Med* 165: 346–347.

Ziambaras, K., Totty, W.A., Teitelbaum, S.L., Dierkes, M. and Whyte, M.P. (1997) Extraskeletal osteoclastomas responsive to dexamethasone treatment in Paget bone disease. *J Clin Endocrinol Metab* 82: 3826–3834.