

CLINICAL PRACTICE

Paget's Disease of Bone

Michael P. Whyte, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 69-year-old man reports increasing pain in the right leg. Physical examination reveals warmth and anterolateral bowing of the right shin. The serum alkaline phosphatase level is 260 U per liter (normal, 38 to 126 U per liter). A skeletal scintigraphic scan reveals enhanced uptake in only the deformed tibia, where a radiograph shows changes indicative of Paget's disease. His sister, whose alkaline phosphatase level is 160 U per liter, has asymptomatic Paget's disease confined to the left iliac wing. How should their conditions be managed?

THE CLINICAL PROBLEM

Paget's disease of bone¹ is a chronic affliction of the adult skeleton featuring one or more areas of aggressive osteoclast-mediated bone resorption preceding imperfect osteoblast-mediated bone repair.^{2,3} This disturbance begins as a wedge of destructive osteoclasts at one end of a bone that slowly but relentlessly advances to disrupt the entire structure.⁴ The deranged skeletal remodeling that follows causes bone expansion and softening, sometimes with pain, fracture, or deformity, and — rarely — neoplastic transformation.^{2,3}

Paget's disease typically manifests in middle or advanced age and is slightly more common in men.^{2,3} The prevalence is highest in Great Britain, Australia, New Zealand, North America, and Western Europe.^{5,6} In the United States, approximately 1 percent of the population over 40 years of age is affected.³ So-called juvenile Paget's disease is an extremely rare autosomal recessive condition characterized by childhood deafness, fractures, and deformity resulting from generalized, lifelong acceleration of bone turnover, usually due to osteoprotegerin deficiency.⁷

Paget's disease typically involves just one bone (monostotic) or a few bones (polyostotic), primarily the skull or pelvis, or a vertebra, femur, or tibia.^{2,3} Osteolytic fronts progress approximately 1 cm yearly⁴ (Fig. 1). Subsequent "mixed-stage" disease features cortical thickening (hyperostosis), disorganized coarse trabeculae (osteosclerosis), and bone expansion.⁸ In cases of advanced ("burnt out") disease, bones are widened and heterogeneously ossified.⁸ Remarkably, this pagetic process does not spread spontaneously to adjacent bones,^{2,3} but there is no cure.

Paget's disease is usually asymptomatic and discovered incidentally.³ Most clinical manifestations are skeletal,⁹ but the prevalence of various signs and symptoms and complications is uncertain.¹⁰ Skeletal expansion or distortion may be obvious if the disease involves the skull, jaw, clavicle,² or a long bone of the leg.¹ Hypervascularity of affected bone may cause palpable warmth.³

Mild-to-moderate, deep, aching bone pain characteristically begins late in the clinical course, persists throughout the day and at rest, and seems worse at night.^{2,3} Achiness in a weakened femur or tibia often intensifies on weight bearing, especially if there are osteolytic lesions.

Acute fractures through pagetic lesions can mend rapidly, although fracture

From the Division of Bone and Mineral Diseases, Washington University School of Medicine at Barnes-Jewish Hospital, and the Center for Metabolic Bone Disease and Molecular Research, Shriners Hospitals for Children — both in St. Louis. Address reprint requests to Dr. Whyte at Shriners Hospitals for Children, 2001 S. Lindbergh Blvd., St. Louis, MO 63131, or at mwhyte@shrinenet.org.

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Figure 1. Lateral Radiograph of the Right Leg of a 69-Year-Old Man with Paget's Disease.

A characteristic osteolytic front, forming a "blade of grass" sign (arrow), has descended the tibia. Subsequent disorganized osseous repair has resulted in bone expansion, a thickened cortex, and patchy areas of osteosclerosis and relative osteopenia. Arterial calcification is also obvious.

malunion in the proximal femur is not uncommon.¹⁰ Chronic, sometimes painful, fissure fractures may occur along convex surfaces of curved bones.² Adjacent joints will be damaged if there is deformity, and osteoarthritis can develop, especially in hips and knees.^{9,11} Osteosarcomas, or other skeletal sarcomas, develop in fewer than 1 percent of patients with Paget's disease but are more common and aggressive than in age-matched controls.¹² Constant and worsening bone pain and sometimes a new mass or sudden fracture should raise concern about malignant transformation.^{2,3}

Neurologic complications — in particular, hearing loss — may result from skull involvement.¹³ Basilar impression (an acquired deformity of the craniocervical region), hydrocephalus with headache and dizziness, and cranial-nerve deficits occur rarely.^{14,15} An increased prevalence of depression was reported on the basis of a survey of members of the Paget Foundation,¹⁶ but this increase is controversial and not supported by other data.¹⁷

In the spine, compression or ischemia ("vascular steal") may cause pain, dysesthesias, or paralysis.¹⁴ However, symptoms resulting from spinal stenosis are uncommon.^{2,3,14} Hypercalcemia is rare, occurring primarily with active, polyostotic disease and immobilization or dehydration; when it is diagnosed, concomitant primary hyperparathyroidism should be ruled out.^{2,3} Although cardiac output may increase according to the extent and activity of Paget's disease, heart failure is atypical.¹⁸ Compression of blood vessels occasionally complicates skeletal expansion. Aortic-valve, endocardial, and arterial calcification¹⁹; nephrolithiasis; and Peyronie's disease have been associated with Paget's disease, but the mechanisms remain unclear.

The cause of Paget's disease is uncertain.^{2,3} Evidence indicates both genetic and environmental influences. Five to 40 percent of patients re-



port that first-degree relatives have the disorder.^{20,21} Heterozygous mutations affecting either of two genes have been documented in Paget's disease. One type of mutation disrupts a single domain of sequestosome 1/p62 and is found especially in French-Canadian patients but also in some familial and sporadic cases in other populations.^{21,22} The other type consists of domain-specific defects within valosin-containing protein that predispose to Paget's disease in a rare syndrome also associated with late-onset inclusion-body myopathy and dementia.²³ Viral infection has also been suggested as having a role in the pathogenesis²⁴ on the basis of observations of particles resembling paramyxovirus nucleocapsids, as well as antigens and nucleic acid sequences of measles virus, canine distemper virus, or respiratory syncytial virus^{25,26} in the nuclei and cytoplasm of pagetic osteoclasts. However, this remains controversial, since these observations have not always been replicated and viruses have not been isolated from lesional tissue.²⁷

STRATEGIES AND EVIDENCE

EVALUATION

Paget's disease is frequently discovered because of elevation in serum alkaline phosphatase levels not explained by aberrations of mineral homeostasis or other skeletal or hepatobiliary disturbances. The disease typically can be diagnosed with plain radiography (Fig. 1) and, in many cases, is first identified on radiographs (often ordered for an unrelated indication).

Most untreated patients have elevated serum total alkaline phosphatase levels,²⁸ which reflect both the extent and the activity of the disease.^{2,3} This measurement usually suffices for biochemical assessment and follow-up, unless a coexisting hepatobiliary disturbance requires assaying the bone-specific isoform.^{3,28} Measuring serum calcium and 25-hydroxyvitamin D levels is reasonable to rule out primary hyperparathyroidism and vitamin D deficiency in the face of an elevated bone alkaline phosphatase level.²⁹ Markers of bone resorption (e.g., urinary deoxypyridinoline and cross-linked N-telopeptide of type I collagen) are more expensive and perform less well.²⁸ However, alkaline phosphatase levels can be normal when there is only a small focus of Paget's disease or after successful medical treatment.

Bone scintigraphy (Fig. 2) followed by radiography of the "hot spots" establishes the skeletal distribution and burden of Paget's disease.³⁰ Enhanced radionuclide uptake represents increased bone formation and blood flow and may appear before radiographic changes. However, mature lesions are sometimes not apparent on scanning because pagetic activity has subsided. Uptake may be further increased, or decreased, if sarcoma develops; plain radiographs may reveal destructive lesions. Further assessment, if malignancy is suspected, includes either computed tomography³ or magnetic resonance imaging,³¹ as well as biopsy.



Figure 2. Skeletal Scintigram of a 67-Year-Old Woman with Paget's Disease.

Shown are typical features of polyostotic Paget's disease, including focally enhanced radionuclide uptake that shows partial, as well as complete, bone involvement.

Positron-emission tomography for identifying malignant conditions may be falsely positive in cases of Paget's disease.³²

If there is uncertainty about the diagnosis of Paget's disease (e.g., if metastatic disease is a possible alternative), a biopsy can be diagnostic, revealing characteristic histopathology (Fig. 3). However, a biopsy is rarely needed, and performing biopsies of weight-bearing lesions could cause fracture.

In some patients with Paget's disease, it is unclear whether pain is due to the bone disorder or to associated osteoarthritis. The response to intraarticular injection of an anesthetic or to a trial of antiresorptive therapy may be informative in such cases.

SUPPORTIVE THERAPY

Asymptomatic Paget's disease diagnosed on the basis of incidental findings often does not require treatment.^{2,3} However, randomized trials of therapy are relatively short-term and have not assessed late complications¹⁰; many aspects of treatment are currently guided by clinical experience.^{2,3}

Difficulties from bowing of the lower limbs, gait disturbances, or spinal stenosis can be helped by shoe lifts, canes, orthotics, or physical therapy.^{2,3,33} Occasional bone or joint aches are likely to respond to acetaminophen or nonsteroidal antiinflammatory drugs. Counseling regarding the prevention of falls and fractures (including avoiding heavy lifting for patients with vertebral involvement) and weight control in obese patients (to reduce pain related to weight bearing) may be useful. Long-bone fractures often require internal fixation that can accelerate a patient's return to ambulation.³³ Complete immobilization may precipitate hypercalcemia, and it should be avoided. Tibial osteotomy to realign the knee may decrease mechanical pain.³⁴ Total joint arthroplasty (usually of the hip³⁵) for osteoarthritis often diminishes joint pain that is unresponsive to medical treatments. Associated spinal stenosis may require neurosurgical intervention.^{2,3} The not-for-profit Paget Foundation is an excellent resource for patient education (www.paget.org).

PHARMACOLOGIC THERAPY

Clinical manifestations of Paget's disease in which pharmacologic therapy is recommended are summarized in Table 1.^{2,3,10,36} Symptomatic disease is the most common indication for pharmacother-

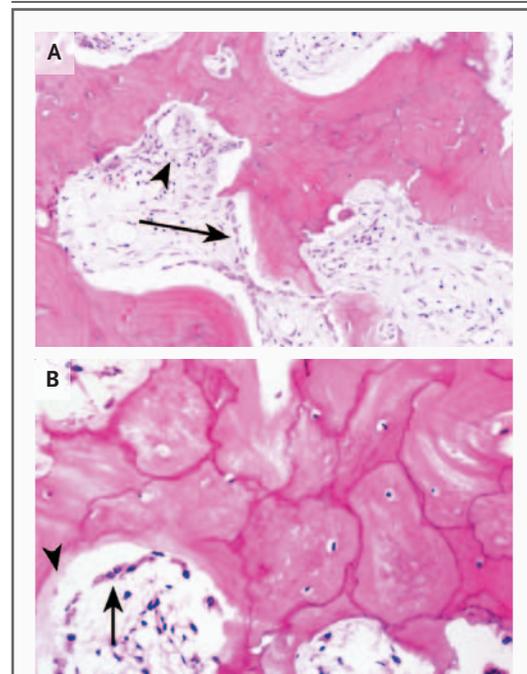


Figure 3. Histopathology of Paget's Disease.

The active phase (Panel A) features disorganized bone architecture with clusters of numerous, large, "hypermultinucleated" osteoclasts (arrowhead) adjacent to many osteoblasts (arrow), which synthesize matrix so rapidly that collagen forms an immature woven or lamellar pattern with faint cement lines. The stroma is vascular and fibrous (hematoxylin and eosin). In Panel B, the late phase features thick trabeculae with a mosaic pattern of prominent, hematoxyphilic, cement lines at the interfaces of the numerous past episodes of bone resorption followed by formation. Osteoblast activity (arrow) remains apparent with pale osteoid deposition (arrowhead) (hematoxylin and eosin).

apy. Randomized trials show that pharmacotherapy can reduce or resolve pagetic pain and elevations in the levels of biochemical markers, improve skeletal scintigraphy, and sometimes heal osteolytic disease and restore normal histologic patterns of bone remodeling.^{2,3} Pharmacotherapy is also used with the goal of preventing or minimizing complications in patients at risk, such as those with active, polyostotic disease near neurovascular structures or major joints, and especially those who are young or who await skeletal surgery. It should be recognized, however, that the efficacy of pharmacotherapy for these indications has not been established in randomized trials. Drugs for Paget's disease include various bisphosphonates and salmon calcitonin (Table 2).

Bisphosphonates

Bisphosphonates are synthetic analogues of inorganic pyrophosphate that are not biodegradable, have skeletal half-lives measured in years, and adhere to mineralized surfaces.³⁷ They are ingested selectively by osteoclasts and disrupt energy metabolism or specific enzymatic pathways.³⁷ Currently, five bisphosphonates have been approved by the Food and Drug Administration (FDA) for the treatment of Paget's disease (Table 2). All are taken orally except pamidronate, which is administered intravenously. In general, these agents are not recommended when the glomerular filtration rate is below 30 to 35 ml per minute per 1.73 m² of body-surface area.

In randomized trials with a duration of less than two years, etidronate or tiludronate normalized elevated alkaline phosphatase levels in approximately one third of patients after initial courses, and reduced the levels by at least 50 percent in most patients.^{38,39} Because etidronate may cause osteomalacia,⁴⁰ this agent is best avoided when osteolytic fronts threaten weight-bearing bones.^{2,3}

As compared with etidronate and tiludronate, alendronate and risedronate are more potent for inhibiting bone turnover and induce more rapid, complete, and sustained biochemical responses.⁴¹⁻⁴⁴ After a first course of treatment, these agents normalize markers of bone turnover in most patients with moderate-to-severe Paget's disease, and most patients report relief of pain.⁴¹⁻⁴⁴ Biochemical remission or nadir can persist for 6 to 18 months and sometimes longer after a single course. Upper gastrointestinal irritation, usually mild and nonspecific, is the major side effect of bisphosphonates, but esophageal ulcers may occur. Etidronate and tiludronate are less likely to cause these side effects than more potent oral agents.⁴⁵ To minimize complications, patients should not recline or exercise for a half hour after dosing. Delayed esophageal emptying is a contraindication to the use of bisphosphonates.

Intravenous administration of pamidronate averts gastrointestinal toxicity and, therefore, is useful for patients who cannot tolerate oral bisphosphonates. In patients who have not previously been treated for Paget's disease, pamidronate and alendronate have similar efficacy for achieving a biochemical remission.⁴³ Approximately one third of patients treated with pamidronate

Table 1. Recommended Indications for Antiresorptive Treatment of Paget's Disease of Bone.

Symptoms resulting from active bone lesions
Bone pain
Headache with skull involvement
Back pain due to pagetic radiculopathy or arthropathy
Other neurologic syndromes
Fissure fractures
Prophylaxis, even in asymptomatic patients, when affected sites and their metabolic hyperactivity suggest risk from progression and complications, such as fracture in weight-bearing long bones or nerve compression
Elective surgery planned for a pagetic site (e.g., hip replacement)
Hypercalcemia resulting from immobilization

have brief, mild, flu-like symptoms (fever, myalgias, headache, and malaise) that are responsive to analgesics and antipyretics. Transient iritis develops in some patients and can also occur, rarely, with other nitrogen-containing bisphosphonates.^{2,3} For moderate-to-severe Paget's disease, the FDA-approved regimen of pamidronate is 30 mg given on three consecutive days for a total dose of 90 mg, although for mild Paget's disease some physicians prescribe one or two 60-mg doses. An intravenous bisphosphonate such as pamidronate may be useful to diminish the vascularity of lesions for untreated patients who will soon undergo elective orthopedic surgery. Because transient hypocalcemia is possible, giving calcium orally at the time of infusions is prudent.²⁹ Extended calcium supplementation may help in healing pagetic lesions, although this has not been rigorously studied.

Intravenous bisphosphonates such as zoledronic acid and olpadronate are still more potent and are being evaluated.¹⁷ The FDA has approved zoledronic acid for hypercalcemia of cancer and disease that metastasizes to the skeleton, and off-label use of the agent for Paget's disease is increasing. Especially rapid and prolonged suppression of markers of bone turnover has been documented, as has improved quality of life, as compared with an oral bisphosphonate.¹⁷ Comparisons of the bisphosphonates are complicated by the use of different doses and durations, which contribute to apparent differences in efficacies.

Extensive and active Paget's disease may require higher doses or more frequent courses of a particular bisphosphonate.^{36,46} Acquired resis-

Table 2. Medications Approved by the Food and Drug Administration for Treatment of Paget's Disease of Bone.

Drug	Recommended Dose and Administration	Side Effects and Cautions
Bisphosphonates		
Etidronate disodium (Didronel)	One 200-to-400-mg tablet orally once daily for 6 mo on the basis of 5 mg/kg of body weight/day*† Course should not exceed 6 mo; repeated courses can be given after rest periods of 6 mo or longer	Not recommended if the glomerular filtration rate is below 30 to 35 ml/min; contraindicated if delayed gastric emptying May cause gastroesophageal irritation including esophagitis (with alendronate or risedronate), osteomalacia (with etidronate), osteonecrosis of the jaw, and iritis (rarely)
Alendronate sodium (Fosamax)	One 40-mg tablet orally once daily for 6 mo*‡	May cause gastroesophageal irritation including esophagitis (with alendronate or risedronate), osteomalacia (with etidronate), osteonecrosis of the jaw, and iritis (rarely)
Tiludronate disodium (Skelid)	Two 200-mg tablets orally once daily for 3 mo*†	
Risedronate sodium (Actonel)	One 30-mg tablet orally once daily for 2 mo*‡	
Pamidronate disodium (Aredia)§	30 mg intravenously over a 4-hr period on 3 consecutive days; the course may be readministered as needed; single infusions of a higher dose are often used instead	Brief, mild, influenza-like symptoms such as fever, myalgias, headache, and malaise; transient hypocalcemia; and short-lived iritis and bone pain Risk of osteonecrosis of the jaw
Salmon calcitonin (Miacalcin)¶	A subcutaneous or intramuscular injection of 50 to 100 U daily or three times a week for 6 to 18 mo	Transient nausea and facial flushing, as well as tachyphylaxis

* Oral bisphosphonates should be taken with 6 to 8 oz of plain water.

† The stomach should be empty for two hours before and for two hours after dosing.

‡ The drug should be taken after an overnight fast. After taking the tablet, the patient should not lie down for at least 30 minutes and should wait at least 30 minutes before eating or drinking anything other than tap water or taking any other medication.

§ Pamidronate is available in 30-mg and 90-mg vials.

¶ Because of insufficient potency, a calcitonin nasal spray has not been approved by the Food and Drug Administration for Paget's disease.

tance to an individual compound is possible but may be overcome by using an alternative bisphosphonate.⁴⁵

Salmon Calcitonin

The use of salmon calcitonin (administered by subcutaneous injection) for Paget's disease has been largely supplanted by the use of bisphosphonates,³⁷ although treatment with salmon calcitonin remains an option if bisphosphonates are not tolerated or contraindicated. Salmon calcitonin typically decreases elevated markers of skeletal turnover by 50 percent, often decreases bone pain and warmth, sometimes improves neurologic complications (including "vascular steal" syndromes), and can heal osteolytic lesions.^{2,3} However, disease reactivation is likely soon after cessation of therapy, acquired resistance occurs in about 25 percent of patients, and bothersome side effects, including nausea and flushing, are common.^{2,3}

ASSESSING PHARMACOLOGIC TREATMENT

Serum alkaline phosphatase levels typically decrease within a few months of initiating therapy. Many clinicians treat with the aim of correcting this marker, although data are lacking to support

a precise target level.^{10,36} Unless osteolysis is apparent, radiographic follow-up is not considered useful, given the heterogeneous appearance of Paget's disease.^{4,8} Quantitative bone scans may be helpful in assessing small pagetic areas when biochemical indexes of skeletal turnover are unremarkable, but such scans are not widely available.³⁰

Treatment is typically repeated if there is a return of symptoms or a rise in serum alkaline phosphatase levels^{2,3} (typically assessed every two to three months at first, and then every six months).^{2,3,47} When alkaline phosphatase values have stabilized near normal levels, some clinicians consider a rise by 25 percent or more to warrant repeated therapy,³⁶ although data are lacking that show that treating such biochemical elevations in the absence of symptoms is beneficial.¹⁰

AREAS OF UNCERTAINTY

Studies from New Zealand and the United Kingdom suggest a decline in the incidence and severity of Paget's disease of bone,^{5,6} although the explanation is uncertain.

Because of a lack of long-term, placebo-controlled trials, it is unknown whether aggressive antiresorptive treatment reduces complications

of Paget's disease; therefore, its use for the prevention of complications remains controversial.¹⁰ Whether maintenance doses of bisphosphonates after a course of therapy might suppress the activity of Paget's disease and improve outcomes requires study. Clinicians often aim to normalize markers of bone remodeling in patients with Paget's disease,³⁶ but it is not known whether this is the optimal target.¹⁰

It is uncertain whether treatment with bisphosphonates should be withheld until acute fractures have healed. Longer-term data are needed to make a better evaluation of the possible risks of prolonged bisphosphonate therapy (e.g., gastroesophageal irritation or potential skeletal toxicities at pagetic sites or elsewhere). One such possible toxicity is "osteonecrosis" of the jaw, which has been described in case reports and series, most in association with prolonged intravenous bisphosphonate therapy for disease that is metastatic to the skeleton, but a few in relation to patients with Paget's disease treated with pamidronate.⁴⁸

GUIDELINES

There are no published guidelines for the management of Paget's disease from American medical societies, but recommendations have come from consensus panels in the United States and Canada.^{49,50} Formal recommendations in the United Kingdom note deficiencies in data and focus on evidence-based interventions; thus, these guidelines do not advocate the use of bisphosphonates for the purposes of preventing complications of Paget's disease.¹⁰

CONCLUSIONS AND RECOMMENDATIONS

The diagnosis of Paget's disease of bone is often suspected on the basis of an elevated serum alkaline phosphatase level and confirmed by radiographic assessment. There is no cure, but randomized trials indicate that antiresorptive treatment reduces associated pain and lowers elevated levels of alkaline phosphatase, a useful marker of disease extent and activity. Therapy with bisphosphonates is used with the goal of preventing complications of Paget's disease (e.g., bowing of the limbs and fracture), although such benefits are unproven.

I would treat the man described in the vignette with a course of oral aminobisphosphonate, and then I would monitor his symptoms and alkaline phosphatase levels to assess whether further therapy is needed. Intravenous bisphosphonate therapy is another option, particularly if oral agents are not well tolerated. I would not recommend antiresorptive therapy for the sister, since she is asymptomatic and has Paget's disease in a bone that is not likely to have symptoms or complications of the disease.

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REFERENCES

- Paget J. On a form of chronic inflammation of bones (osteitis deformans). *Trans Med-Chir Soc* 1877;60:37-63.
- Kanis J. Pathophysiology and treatment of Paget's disease of bone. 2nd ed. London: Martin Dunitz, 1998.
- Altman R. Paget's disease of bone. In: Coe FL, Favus MJ, eds. *Disorders of bone and mineral metabolism*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2002: 985-1020.
- Doyle FH, Banks LM, Pennock JM. Radiologic observations on bone resorption in Paget's disease. *Arthritis Rheum* 1980; 23:1205-14.
- Doyle T, Gunn J, Anderson G, Gill M, Cundy T. Paget's disease in New Zealand: evidence for declining prevalence. *Bone* 2002;31:616-9.
- Van Staa TP, Selby P, Leufkens HG, Lyles K, Sprafka JM, Cooper C. Incidence and natural history of Paget's disease of bone in England and Wales. *J Bone Miner Res* 2002;17:465-71.
- Whyte MP, Obrecht SE, Finnegan PM, et al. Osteoprotegerin deficiency and juvenile Paget's disease. *N Engl J Med* 2002; 347:175-84.
- Smith SE, Murphey MD, Motamedi K, Mulligan ME, Resnik CS, Gannon FH. Radiologic spectrum of Paget disease of bone and its complications with pathologic correlation. *Radiographics* 2002;22:1191-216.
- Altman RD. Musculoskeletal manifestations of Paget's disease of bone. *Arthritis Rheum* 1980;23:1121-7.
- Selby PL, Davie MW, Ralston SH, Stone MD. Guidelines on the management of Paget's disease of bone. *Bone* 2002;31:366-73. [Erratum, *Bone* 2002;31:437.]
- Helliwell PS, Porter G. Controlled study of the prevalence of radiological osteoarthritis in clinically unrecognised juxta-articular Paget's disease. *Ann Rheum Dis* 1999;58:762-5.
- Grimer RJ, Cannon SR, Taminiau AM, et al. Osteosarcoma over the age of forty. *Eur J Cancer* 2003;39:157-63.
- Monsell EM. The mechanism of hearing loss in Paget's disease of bone. *Laryngoscope* 2004;114:598-606.
- Poncelet A. The neurologic complications of Paget's disease. *J Bone Miner Res* 1999;14:Suppl 2:88-91.
- Chitnavis BP. Reversible dementia in Paget's disease. *J R Soc Med* 2001;94:157-8.

16. Gold DT, Burchett BM, Ship KM, Pieper CF, Lyles KW. Factors associated with self-rated health in patients with Paget's disease of bone. *J Bone Miner Res* 1999;14: Suppl 2:99-102.
17. Reid IR, Miller P, Lyles K, et al. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. *N Engl J Med* 2005;353:898-908.
18. Morales-Piga AA, Moya JL, Bachiller FJ, Munoz-Malo MT, Benavides J, Abaira V. Assessment of cardiac function by echocardiography in Paget's disease of bone. *Clin Exp Rheumatol* 2000;18:31-7.
19. Laroche M, Delmotte A. Increased arterial calcification in Paget's disease of bone. *Calcif Tissue Int* 2005;77:129-33.
20. Siris ES, Ottman R, Flaster E, Kelsey JL. Familial aggregation of Paget's disease of bone. *J Bone Miner Res* 1991;6:495-500.
21. Takata S, Yasui N, Nakatsuka K, Ralston SH. Evolution of understanding of genetics of Paget's disease of bone and related diseases. *J Bone Miner Metab* 2004;22:519-23.
22. Cavey JR, Ralston SH, Hocking LJ, et al. Loss of ubiquitin-binding associated with Paget's disease of bone p62 (SQSTM1) mutations. *J Bone Miner Res* 2005;20:619-24.
23. Watts GD, Wymer J, Kovach MJ, et al. Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. *Nat Genet* 2004;36:377-81.
24. Roodman GD, Windle JJ. Paget disease of bone. *J Clin Invest* 2005;115:200-8.
25. Basle MF, Fournier JG, Rozenblatt S, Rebel A, Bouteille M. Measles virus RNA detected in Paget's disease bone tissue by in situ hybridization. *J Gen Virol* 1986;67:907-13.
26. Gordon MT, Mee AP, Anderson DC, Sharpe PT. Canine distemper virus transcripts sequenced from pagetic bone. *Bone Miner* 1992;19:159-74.
27. Helfrich MH, Hobson RP, Grabowski PS, et al. A negative search for a paramyxoviral etiology of Paget's disease of bone: molecular, immunological, and ultrastructural studies in UK patients. *J Bone Miner Res* 2000;15:2315-29.
28. Eastell R. Biochemical markers of bone turnover in Paget's disease of bone. *Bone* 1999;24:Suppl 5:49S-50S.
29. Rosen CJ, Brown S. Severe hypocalcemia after intravenous bisphosphonate therapy in occult vitamin D deficiency. *N Engl J Med* 2003;348:1503-4.
30. Fogelman I, Carr D, Boyle IT. The role of bone scanning in Paget's disease. *Metab Bone Dis Relat Res* 1981;3:243-54.
31. Sundaram M, Khanna G, El-Khoury GY. T1-weighted MR imaging for distinguishing large osteolysis of Paget's disease from sarcomatous degeneration. *Skeletal Radiol* 2001;30:378-83.
32. Spieth ME, Kasner DL, Manor WF. Positron emission tomography and Paget disease: hot is not necessarily malignant. *Clin Nucl Med* 2003;28:773-4.
33. Hadjipavlou AG, Gaitanis IN, Kontakis GM. Paget's disease of the bone and its management. *J Bone Joint Surg Br* 2002;84:160-9.
34. Parvizi J, Frankle MA, Tiegs RD, Sim FH. Corrective osteotomy for deformity in Paget disease. *J Bone Joint Surg Am* 2003;85:697-702.
35. Kirsh G, Kligman M, Roffman M. Hydroxyapatite-coated total hip replacement in Paget's disease: 20 patients followed for 4-8 years. *Acta Orthop Scand* 2001;72:127-32.
36. Siris ES. Goals of treatment for Paget's disease of bone. *J Bone Miner Res* 1999;14:Suppl 2:49-52.
37. Licata AA. Discovery, clinical development, and therapeutic uses of bisphosphonates. *Ann Pharmacother* 2005;39:668-77.
38. Altman RD. Long-term follow-up of therapy with intermittent etidronate disodium in Paget's disease of bone. *Am J Med* 1985;79:583-90.
39. Roux C, Gennari C, Farrerons J, et al. Comparative prospective, double-blind, multicenter study of the efficacy of tiludronate and etidronate in the treatment of Paget's disease of bone. *Arthritis Rheum* 1995;38:851-8.
40. MacGowan JR, Pringle J, Morris VH, Stamp TC. Gross vertebral collapse associated with long-term disodium etidronate treatment for pelvic Paget's disease. *Skeletal Radiol* 2000;29:279-82.
41. Siris E, Weinstein RS, Altman R, et al. Comparative study of alendronate versus etidronate for the treatment of Paget's disease of bone. *J Clin Endocrinol Metab* 1996;81:961-7.
42. Reid IR, Nicholson GC, Weinstein RS, et al. Biochemical and radiologic improvement in Paget's disease of bone treated with alendronate: a randomized, placebo-controlled trial. *Am J Med* 1996;101:341-8. [Erratum, *Am J Med* 1997;102:322.]
43. Walsh JP, Ward LC, Stewart GO, et al. A randomized clinical trial comparing oral alendronate and intravenous pamidronate for the treatment of Paget's disease of bone. *Bone* 2004;34:747-54.
44. Siris ES, Chines AA, Altman RD, et al. Risedronate in the treatment of Paget's disease of bone: an open label, multicenter study. *J Bone Miner Res* 1998;13:1032-8.
45. Lyles KW. What is "resistance" in Paget's disease of bone? *Arthritis Rheum* 2003;48:2097-9.
46. Rendina D, Mossetti G, Viceconti R, Sorrentino M, Nunziata V. 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* 2004;75:189-96.
47. Alvarez L, Peris P, Guanabens N, et al. Long-term biochemical response after bisphosphonate therapy in Paget's disease of bone: proposed intervals for monitoring treatment. *Rheumatology (Oxford)* 2004;43:869-74.
48. Woo SB, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006;144:753-61.
49. Lyles KW, Siris ES, Singer FR, Meunier PJ. A clinical approach to the diagnosis and management of Paget's disease of bone. *J Bone Miner Res* 2001;16:1379-87.
50. Drake WM, Kendler DL, Brown JP. Consensus statement on the modern therapy of Paget's disease of bone from a Western Osteoporosis Alliance Symposium. *Clin Ther* 2001;23:620-6.

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