AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS | AMERICAN COLLEGE OF ENDOCRINOLOGY

Paget's Disease of Bone

BONE RESOURCE CENTER | BONE.AACE.COM

A Common Bone Disorder

- Paget's disease of bone (PDB), also known as osteitis deformans, is a common disorder characterized by focal areas of increased and disorganized bone remodeling. It may involve a single bone or multiple bones.
- Paget's disease is the second most common bone remodeling disease after osteoporosis, occurring in 1%-2% of white adults older than 55. It primarily affects people of European descent and rarely affects Africans, Asians, or people from the Indian subcontinent. It is slightly more common in men than women. An analysis of data from the National Health and Nutrition Examination Survey (NHANES) reported the overall prevalence of PDB in the United States was at least 1% and perhaps as much as 2% of the general population.

Ralston, SH. Paget's Disease of Bone. *N Engl J Med* 2013; 368:644-650.
Shaker JL. Paget's disease of bone: A review of epidemiology, pathophysiology, and management. *Therapeutic Advances in Musculoskeletal Disease* 2009; 1(2):107-125
Altman RD et al. Prevalence of Pelvic Paget's Disease of Bone in the United States. *Journal of Bone and Mineral Research* 2000; 15(3):461-65.

Probable Genetic Component

- Family history is positive in 15%-30% of patients with PDB, and first-degree relatives of individuals with PDB are about seven times more likely to develop the disease, suggesting a genetic component.
- Up to 50% of patients with a family history and 10% of patients with sporadic PDB carry mutations in the SQSTM1 gene. This gene encodes p62, a protein with a key role in regulating osteoclast function. Other genetic variants have been linked with PDB, most of these in genes involved in osteoclast differentiation and function.

Ralston, SH. Paget's Disease of Bone. *N Engl J Med* 2013; 368:644-650.
Shaker JL. Paget's disease of bone: A review of epidemiology, pathophysiology, and management. *Therapeutic Advances in Musculoskeletal Disease* 2009; 1(2):107-125

Possible Viral Component

- Paget's disease may also have a viral component, although the evidence for this is not definitive. In the osteoclasts of patients with PDB, intranuclear inclusion bodies resembling paramyxovirus nucleocapsids have been observed. The identity of these structures is uncertain, however. They may represent abnormal protein aggregates resulting from defects of the autophagy pathway.
- Paramyxoviruses are the most extensively studied potential environmental agents for PDB, particularly the canine distemper and measles virus. However, whether viruses play a role in the development of PDB is still controversial.

Ralston, SH. Paget's Disease of Bone. *N Engl J Med* 2013; 368:644-650.
Shaker JL. Paget's disease of bone: A review of epidemiology, pathophysiology, and management. *Therapeutic Advances in Musculoskeletal Disease* 2009; 1(2):107-125

Clinical Presentation

- PDB is a chronic, progressive disease that preferentially targets the axial skeleton. It most commonly affects the pelvis (70% of cases), femur (55%), lumbar spine (53%), skull (42%), and tibia (32%).
- Skeletal lesions of PDB are characterized by increased osteoclastic bone resorption, increased but somewhat disorganized bone formation, and increased vascularity of bone. Bones affected by PDB are weakened and at increased risk for fracture.

National Institutes of Health. Paget's Disease of Bone. Available at https://www.bones.nih.gov/health-info/bone/pagets. Accessed September 7, 2018.
Ralston, SH. Paget's Disease of Bone. *N Engl J Med* 2013; 368:644-650.
Shaker JL. Paget's disease of bone: A review of epidemiology, pathophysiology, and management. *Therapeutic Advances in Musculoskeletal Disease* 2009; 1(2):107-125

Clinical Presentation, continued…

- Most patients with PDB are asymptomatic. The first indication is often an elevated serum alkaline phosphatase level or an abnormal radiograph in a patient whose health is being investigated for other reasons.
- The most common symptom is bone pain, likely due to increased bone turnover or a complication such as osteoarthritis, spinal stenosis, or pseudofracture. Approximately 40% of patients present with bone pain.
- Other symptoms include bone deformity, warmth of skin overlying an affected bone, secondary arthritis, and headaches or hearing loss if PDB affects the skull.

National Institutes of Health. Paget's Disease of Bone. Available at https://www.bones.nih.gov/health-info/bone/pagets. Accessed September 7, 2018.
Ralston, SH. Paget's Disease of Bone. *N Engl J Med* 2013; 368:644-650.
Shaker JL. Paget's disease of bone: A review of epidemiology, pathophysiology, and management. *Therapeutic Advances in Musculoskeletal Disease* 2009; 1(2):107-125

Complications of PDB

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

Shaker JL. Paget's disease of bone: A review of epidemiology, pathophysiology, and management. *Therapeutic Advances in Musculoskeletal Disease* 2009; 1(2):107-125. PAGE 111

Diagnosis

- Paget's disease can be diagnosed with radiographs of suspicious regions of the skeleton showing the typical features of the disease. If PDB is found, a baseline bone scan is recommended to detect possible asymptomatic areas of disease that might not have been identified in the original imaging.
- The use of magnetic resonance imaging or computed tomography is not usually necessary, although these imaging techniques can be useful in patients with suspected complications such as spinal stenosis or osteosarcoma.
- Patients with PDB typically present with an isolated elevation in the alkaline phosphatase (ALP) level, with otherwise normal results of biochemical testing. After a radiologic diagnosis of PDB, The Endocrine Society recommends an initial biochemical evaluation of serum total ALP or a more specific marker of bone formation when appropriate.
- Liver function and Gamma-Glutamyl Transferase (GGT) tests can be used to rule out other potential causes of elevated ALP. Bone-specific ALP can confirm a diagnosis.

Singer FR et al. Paget's disease of bone: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2014; 99(12):4408-4422.
Ralston, SH. Paget's Disease of Bone. *N Engl J Med* 2013; 368:644-650.

Diagnosis

- Patients should be evaluated for other potential causes of bone pain and PDB symptoms, including the following:
  - Increased metabolic activity
  - A complication such as osteoarthritis or osteomalacia
  - Another coexisting musculoskeletal condition
  - Primary hyperparathyroidism
  - Malignancy

Treatment

- The drugs of first choice for treating PDB are nitrogen-containing bisphosphonates (aminobisphosphonates) such as alendronate, pamidronate, risedronate, and zoledronic acid. These drugs preferentially target affected sites and are highly effective at suppressing the increased bone turnover characteristic of the disease.
- The main indication for treatment is bone pain. Treatment can also be considered for managing Pagetic involvement of vulnerable areas, decreasing vascularity in a particular affected area before surgery, and to relieve neurologic symptoms.
- The Endocrine Society recommends a single 5-mg intravenous dose of zoledronic acid as the treatment of choice in patients without contraindications. This recommendation is based on two clinical trials that compared one 15-minute infusion of 5 mg of zoledronic acid with 60 days of oral risedronate (30 mg per day). At 6 months, therapeutic response, ALP levels, onset of action, pain relief, and quality of life were significantly better in the zoledronic acid group.

Reid IR et al. Comparison of a Single Infusion of Zoledronic Acid with Risedronate for Paget's Disease. N Engl J Med 2005; 353:898-908.
Singer FR et al. Paget's disease of bone: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2014; 99(12):4408-4422.
Ralston, SH. Paget's Disease of Bone. *N Engl J Med* 2013; 368:644-650.

Treatment Side Effects

- Intravenous bisphosphonates can cause transient bone pain, myalgia, headache, nausea, pyrexia, and fatigue 1 to 3 days after the infusion. These acute-phase symptoms almost always subside within a week, even without treatment. However, acetaminophen administered before and for a few days after the infusion can ameliorate the symptoms. They are less common after second and subsequent infusions.
- Hypocalcemia may also develop in patients treated with intravenous bisphosphonates, especially those with substantial elevations in bone turnover and vitamin D deficiency. The risk can be minimized by correcting vitamin D deficiency and calcium deficiency before the infusion, and by continuing appropriate vitamin D and calcium supplements after the infusion.

Ralston, SH. Paget's Disease of Bone. *N Engl J Med* 2013; 368:644-650.

Assessing Treatment Response

- If there is urgent need to control symptoms or if the disease is particularly active, The Endocrine Society suggests using short-term response of bone resorption markers before and shortly after treatment to assess therapeutic response.
- In patients with osteolytic lesions of PDB, the society recommends a repeat x-ray approximately 1 year after radiological diagnosis to assess whether there has been improvement with therapy.
- Follow-up ALP testing is recommended every 3-6 months. Additional treatment can be considered if symptoms persist or return after treatment, or if ALP levels rise above normal after having been suppressed.

Singer FR et al. Paget's disease of bone: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2014; 99(12):4408-4422.